ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ACE INHIBITORS TO SACUBITRIL/VALSARTAN

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BY

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TO

MY

FAMILY

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ABSTRACT

Introduction: A new therapeutic class of agents acting on the RAAS and the neutral endopeptidase system has been developed [angiotensin receptor neprilysin inhibitor (ARNI)] which have been shown to improve survival in patients with HFrEF.

Aim of Study: To access effects of ARNI (SACUBITRIL/VALSARTAN) therapy on clinical parameters and echocardiographic features in HFrEF patients as compared to ace inhibitors.

Materials & Methods: The study was performed on 100 patients with HFrEF(EF<40%) who were already on ACE inhibitors in addition to optimal medical therapy. All patients were analysed at baseline by NYHA functional class, 6 minute walk test and transthoracic echocardiography (TTE) and after 6 months of ACE-I therapy. At 6 months of study, all patients were given option for sacubitril/valsartan therapy and those who opted were switched to sacubitril/valsartan after washout period of 36 hours while remaining patients continued on ACE-I therapy. Thereafter, both the groups were followed up for 6 months and compared for clinical and echocardiographic parameters.

Results: 55 patients in ACE-I group and 31 patients in ARNI group completed the study. Significantly greater improvement in NYHA class and 6 minute walk distance was noted with ARNI therapy compared to ACE-I therapy ($p<0.05$). Echo parameters such as ejection fraction, left ventricle internal diameter systole and diastole, Left atrial diameter, mitral regurgitation severity showed significant improvement with ARNI therapy in comparison to ACE-I therapy ($p<0.05$).

Conclusion: ARNI therapy resulted in greater and significant reverse remodeling and improvement in functional status in comparison to ACE-I therapy in patients with Heart failure and reduced EF.

Keywords: ARNI, Sacubitril/Valsartan, HFrEf, NYHA, ace inhibitors.

ABBREVATIONS

6MWT	6 minute walk test
ACE-I	Angiotensin converting enzyme inhibitors
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
AF	Atrial fibrillation
BNP	Brain natriuretic peptide
CAD	coronary artery disease
CABG	Coronory artery bypass graft
CCB	Calcium channel blockers
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CVA	Cerebrovascular accident
CRR	Cardiac reverse remodeling
DCMP	Dilated cardiomyopathy
DIFF	Difference
DM	Diabetes mellitus
DOE	Dyspnea on exertion
ECG	Electrocardiogram
EROA	Effective regurgitant orifice area
GDMT	Guideline directed medical therapy
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HRpEF	Heart failure with preserved ejection fraction
HOSP	Hospitalization
HTN	Hypertension
ICMP	Ischaemic cardiomyopathy
ICD	Implantable cardioverter‐defibrillators

CRT	cardiac resynchronization therapy
CAD	coronary artery disease
LA	Left atrium
LV	Left ventricle
LVAD	left ventricular assist devices
LVEF	left ventricular ejection fraction
LVIDd	Left ventricle internal diameter diastole
LVIDs	Left ventricle internal diameter systole
LVESD	Left ventricular end systolic diameter
LVESV	Left ventricular end systolic volume
LVEDD	Left ventricular end diastolic diameter
LVEDV	Left ventricular end diastolic volume
MR	Mitral regurgitation
MRAs	Mineralocorticoid receptor antagonists
MORT	Mortality
MI	Myocardial infarction
MV	Mitral valve
NICMP	Non ischaemic cardiomyopathy
NYHA	New York Heart Association
No.	Number
NPs	Natriuretic peptides
NT-proBNP	N-terminal pro-BNP
PASP	Pulmonary artery systolic pressure
OMT	Optimal medical therapy
RAAS	Renin angiotensin aldosterone system
RV	Right ventricle
SD	Standard deviation
SNS	sympathetic nervous system
TAPSE	Tricuspid annular plane systolic excursion
TTE	Transthoracic echocardiography

KEYS TO MASTER CHART

6M	6 months
6-12M	6 -12 months
ACE-I	Angiotensin converting enzyme inhibitors
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
BNP	Brain natriuretic peptide
CAD	coronary artery disease
CABG	Coronory artery bypass graft
CCB	Calcium channel blockers
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CRT	Cardiac resynchronization therapy
CVA	Cerebrovascular accident
DCMP	Dilated cardiomyopathy
DOE	Dyspnoea on exertion
ECG	Electrocardiogram
EF	Ejection fraction
HOSP	Hospitalization
HTN	Hypertension
ICD	Implantable cardioverter defibrillator
ICMP	Ischaemic cardiomyopathy
IVCD	Interventricular conduction defect
LA	Left atrium
LAFB	Left anterior fascicular block
LBBB	Left bundle branch block
LVIDd	Left ventricle internal diameter diastole
LVIDs	Left ventricle internal diameter systole
MORT	Mortality
MR	Mitral regurgitation
MRA	Mineralocorticoid receptor antagonist
MRD. No	Medical record department number
MOD	Moderate
MV	Mitral valve
NCLV	Noncompaction left ventricle
NSR	Normal sinus rythum
NYHA	New York Heart Association
PASP	Pulmonary artery systolic pressure
PPI	Permanent pacemaker insertion
RBBB	Right bundle branch block

Sr. No	Serial number
TAPSE	Tricuspid annular plane systolic excursion

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INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.

The main terminology used to describe HF is historical and is based on measurement of the LVEF. HF comprises a wide range of patients, from those with normal LVEF [typically considered as ≥50%; HF with preserved EF (HFpEF)] to those with reduced LVEF [typically considered as <40%; HF with reduced EF (HFrEF)]. Patients with an LVEF in the range of 40–49% represent a „grey area", which is now defined as HFmrEF.[1]

The prevalence of HF is approximately 1–2% of the adult population in developed countries, rising to ≥10% among people >70 years of age.[2] The lifetime risk of HF at age 55 years is 33% for men and 28% for women.[3] The 12-month all-cause mortality rates for hospitalized and stable/ambulatory HF patients were 17% and 7%, respectively.[4] In patients with HF (both hospitalized and ambulatory), most deaths are due to cardiovascular causes, mainly sudden death and worsening HF. All-cause mortality is generally higher in HFrEF than HFpEF.[5]

Heart failure is a major health problem in India with current estimate regarding incidence of heart failure ranging in between 1.3 to 23 million.[6] Trivandrum Heart Failure Registry (THFR) reported in hospital mortality of 9.7% for patients with HfrEF and 4.8% for HfpEF. 3 yr mortality for patients with heart failure was 44.8%. The INTER-CHF study reported 23% 1 yr mortality in patients of heart failure in India.[7] Also, the mean age of patients presenting with heart failure is decade younger with much higher mortality than western countries. Medication adherence ranges from 25% to 50%, and the tolerance of guideline based medication is low

for Indian patients. Devices such as implantable cardioverter‑defibrillators (ICD) and cardiac resynchronization therapy (CRT) devices and left ventricular assist devices (LVAD) are available but not within the reach of all.[8]

The NYHA functional classification has been used to describe the severity of symptoms and exercise intolerance.[9] For patients presenting with symptoms or signs for the first time, non-urgently in primary care or in a hospital outpatient clinic , the probability of HF should first be evaluated based on the patient's prior clinical history [e.g. coronary artery disease (CAD), arterial hypertension, diuretic use], presenting symptoms (e.g. orthopnoea), physical examination (e.g. bilateral oedema, increased jugular venous pressure, displaced apical beat) and resting ECG. If all elements are normal, HF is highly unlikely and other diagnoses need to be considered. If at least one element is abnormal, plasma natriuretic peptides (NPs) should be measured, if available, to identify those who need echocardiography (an echocardiogram is indicated if the NP level is above the exclusion threshold or if circulating NP levels cannot be assessed).[10] The upper limit of normal in the non-acute setting forB-type natriuretic peptide (BNP) is 35 pg/mL and for N-terminal pro-BNP (NT-proBNP) it is 125 pg/mL; in the acute setting, higher values should be used [BNP , 100 pg/mL, NT-proBNP , 300 pg/mL]. At the exclusionary cut-points, the negative predictive values are very similar and high (0.94–0.98) in both the non-acute and acute setting, but the positive predictive values are lower both in the non-acute setting (0.44–0.57) and in the acute setting (0.66–0.67).[11]Therefore, the use of NPs is recommended for ruling-out HF, but not to establish the diagnosis.

Transthoracic echocardiography (TTE) is the method of choice for assessment of myocardial systolic and diastolic function of both left and right ventricles. For measurement of left ventricular ejection fraction (LVEF), the modified biplane Simpson's rule is recommended.[12] Measurement of regional wall motion abnormalities might be particularly

relevant for patients suspected of CAD or myocarditis. Doppler techniques allow the calculation of haemodynamic variables, such as stroke volume index and cardiac output, based on the velocity time integral at the LV outflow tract area.

Neuro-hormonal antagonists (ACEIs, MRAs and beta-blockers) have been shown to improve survival in patients with HFrEF and are recommended for the treatment of every patient with HFrEF, unless contraindicated or not tolerated. A new therapeutic class of agents acting on the RAAS and the neutral endopeptidase system has been developed [angiotensin receptor neprilysin inhibitor (ARNI)].The first in class is LCZ696 (sacubitril/valsartan), which is a molecule in which the activity of an ARB is favorably integrated and complemented by the combination with sacubitril, capable of enhancing the vasodilator, anti-adrenergic, and anti-apoptotic properties of the natriuretic peptide system as well as its action in antagonizing the rise in ventricular filling pressures. In the setting of volume expansion or pressure overload, the resulting wall stress promotes synthesis of pre-proB-type natriuretic peptide in the ventricular myocardium. [13] Subsequently, the peptide is cleaved first to proBNP, then to the biologically active B-type natriuretic peptide (BNP) and the inactive fragment, amino-terminal (NT)-proBNP.[14] It is also known that the release of BNP induces improved myocardial relaxation and plays an important regulatory role in response to acute increases in ventricular volume by antagonizing the vasoconstriction, sodium retention, and antidiuretic effects of the activated RAAS [15]. It was found that the favorable vasodilatory and natriuretic properties of natriuretic peptides are not sufficient to counteract the noxious effect of RAAS hyperactivation in a significant percentage of cases.[16] Destruction and rapid molecular degradation of BNP, which is carried out by a neutral endopeptidase known as neprilysin, renders the functions exerted by BNP rather ephemeral and of overall modest significance.

Sacubitril is a prodrug that is activated to sacubitrilat by de-ethylation via esterases. [17] Sacubitrilat inhibits the enzyme neprilysin, which is responsible for the degradation of both atrial and B-type natriuretic peptides, hence prolonging half-life of natriuretic peptides to achieve an enhancement of their counter-regulating effects, primarily consisting in lowering ventricular filling pressures and promoting diuresis and natriuresis, so as to antagonize the sympatho-adrenergic system and RAAS. Neprilysin is involved in metabolism of angiotensin II. Inhibition of neprilysin increases angiotensin II thereby potentiating the RAAS and neutralizing the advantages of natriuretic peptide augmentation. Hence, there is need of concomitant RAAS blockade with ARB. [18] Sacubitril/valsartan is currently recommended to replace ACEIs in ambulatory HFrEF patients who remain symptomatic despite optimal medical therapy. The above medications should be used in conjunction with diuretics in patients with symptoms and/or signs of congestion. The use of diuretics should be modulated according to the patient's clinical status.[19]

Oral bioavailability of SACUBITRIL/VALSARTAN is >=60%.Steady-state is reached in 3 days. It is highly protein bound 94-97%. Volume of distribution is 75 L for sacubitril and 103 L for valsartan. Sacubitril component is primarily excreted in the urine (52-68%) and feces (37-48%) Valsartan component is primarily excreted in the feces (86%) and to a lesser extent in the urine (13%).

However, some relevant safety issues remain when initiating therapy with this drug in clinical practice. Neprilysin also catalyzes the degradation process of several other peptides, including bradykinin, a flogosis mediator whose massive release can cause vasodilation, angioedema, and airway obstruction. This concomitant blockade of bradykinin degradation has, however, proved to be much more intense and dangerous when it is associated with the use of omapatrilat compared with sacubitril/valsartan. Omapatrilat was first combined angiotensin converting

enzyme inhibitor and neprilysin inhibitor. When omapatrilat was used as an investigational drug, it caused numerous cases of severe angioedema involving the glottis with obstruction of the upper airways.[20] Therefore, safety concerns about the high incidence of iatrogenic angioedema prevented omapatrilat from being validated by the FDA as a therapeutic agent for cardiac failure. Furthermore, omapatrilat was not found to be superior to enalapril in improving the primary endpoint of death and hospitalization for HF. However, safety data of the PARADIGM HF study showed that the incidence of angioedema with sacubitril/valsartan was 0.5% as opposed to 0.2% with enalapril.[21] Therefore, the acceptable impact of this side effect associated with sacubitril made it possible to dispel the important safety concerns that had previously led regulatory authorities to deny the entrance of omapatrilat on the market. If angioedema occurs, sacubitril/valsartan should be discontinued and should not be rechallenged. Sacubitril/Valsartan should not be used in those with a history of angioedema related to previous ace inhibitor or arb therapy. If switching to or from an ace inhibitor, a 36-hour washout period is required between drugs. Combined treatment with an ace-i (or arb) and sacubitril/valsartan is contraindicated. Symptomatic hypotension was more often present in the sacubitril/valsartan group although there was no increase in the rate of discontinuation. Being a RAAS blocking agent; sacubitril/valsartan may cause impaired renal function in high risk individuals including those with renal artery stenosis. Because of RAAS blockade, sacubitril/valsartan may cause hyperkalemia. There are additional concerns about its effects on the degradation of beta-amyloid peptide in the brain, which could theoretically accelerate amyloid deposition.[22]

Although the physiological mechanisms of action of Sacubitril/Valsartan are well described, its effects on left ventricular remodeling and left ventricular ejection fraction have not been well studied. The goal of our

study is to evaluate the effects of Sacubitril/Valsartan on clinical status and echocardiographic parameters among patients with HFrEF.

AIMS AND OBJECTIVES

1. To study clinical and echocardiographic features in systolic heart failure patients on ACE INHIBITORS.
2. Assessment of clinical and echocardiographic features when patients were switched over from ACE INHIBITORS to SACUBITRIL/VALSARTAN therapy and comparison between two groups.

REVIEW OF LITERATURE

Approximately half of the worldwide HF population has HF with reduced ejection fraction. In these patients, neurohormonal activation is recognized as playing a critical role in the development and progression of their disease.[23] Systems such as the renin angiotensin aldosterone system (RAAS) and sympathetic nervous system (SNS) are activated early in the course of the disease in response to myocardial injury or increases in load on the heart. As HF progresses, neurohormonal activation intensifies and circulating levels of the main effector molecules of these systems are increased in a step-wise manner.[24] Down-stream effects of angiotensin II, aldosterone and the catecholamines, the major signaling molecules of the RAAS and SNS, promote vasoconstriction and salt and water retention. They also stimulate maladaptive cardiac remodeling, a process characterized by increases in cardiac chamber volumes, muscle mass and interstitial fibrosis.[25] Conformational changes in the remodeled left ventricle which becomes more spherical in shape reduces mechanical efficiency and leads to the development of mitral valvular regurgitation. Positive feedback loops between neurohormonal systems further enhance these adverse effects. The net effect is a vicious cycle that results in progressive deterioration in cardiac structure and function and ultimately to the clinical events, including sudden cardiac death, premature mortality and repeated hospitalizations. Hence, cardiac remodeling represents an important target for HF therapy.

Cardiac reverse remodeling (CRR) refers to improvements in damaged ventricular/atrial volume, dimension, and shape.[26] Previous studies reported that inhibition of RAAS improved LVEF and antagonized cardiac remodeling, as well as reducing the risk of cardiovascular death in HFrEF patients.[27] The PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial revealed that a combined angiotensin receptor blocker-

neprilysin inhibitor sacubitril/valsartan markedly decreased cardiovascular and all-cause mortality in patients with HFrEF compared with the ACEI enalapril.[21] This breakthrough promoted ARNI use in HFrEF patients and the findings of preclinical trials have suggested that ARNI may improve the prognoses of HFrEF patients in terms of cardiac fibrosis and cardiomyocyte hypertrophy.[28] ARNI augmented the inhibitory effects of valsartan alone by increasing the systemic exposure to valsartan by 40%, suggesting that ARNI would have greater antiremodeling effects than either valsartan or neprilysin inhibitor alone.

The PARADIGM-HF trial conducted by **John J.V. McMurray *et al* in year 2014**, compared the angiotensin receptor–neprilysin inhibitor sacubitril/ valsartan with enalapril in patients who had heart failure with a reduced ejection fraction. In this double-blind trial, they randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either sacubitril/valsartan (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure. Trial was stopped early after a median follow up of 27 months, because the boundary for an overwhelming benefit with sacubitril/valsartan had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the sacubitril/valsartan group and 1117 patients (26.5%) in the enalapril group (hazard ratio, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001). As compared with enalapril, sacubitril/valsartan also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P = 0.001). Regarding

safety concerns, fewer patients stopped their study medication overall or because of an adverse event in the sacubitril/valsartan group than in the enalapril group. Because of its greater vasodilator effects, treatment with sacubitril/valsartan was associated with a higher rate of symptomatic hypotension (14% vs 9.2%, p<0.001), but there was no increase in the rate of discontinuation because of possible hypotension-related adverse effects. Although the greater hypotensive effect of sacubitril/valsartan might impair renal perfusion, clinically important increases in the serum creatinine level and discontinuation of the study drug because of renal impairment were less frequent in the sacubitril/valsartan group than in the enalapril group. Incidnce of hyperkalemia was also lower in sacubitril/valsartan in comparison to enalapril (4.3 vs 5.6 p=0.007). Sacubitril/valsartan was not associated with an increased risk of serious angioedema. This study provided strong evidence that combined inhibition of the angiotensin receptor and neprilysin is superior to inhibition of the renin–angiotensin system alone in patients with chronic heart failure. [21]

AwsAlmufleh et al in year 2017 performed a single center, retrospective, cohort study with a goal to evaluate the effects of Sacubitril/Valsartan on LVEF and reverse remodeling parameters among patients with HFrEF (n=48) who were treated with Sacubitril/Valsartan for a median duration of 3 months. Clinical and echocardiographic parameters were reviewed at three time points (pre-baseline which was median of 18 months before starting Sacubitril/Valsartan, baseline before treatment started, and post-Sacubitril/Valsartan). Majority of patients were on all guideline directed optimal heart failure therapy with 97.5% on BBs and 87.5% on MRAs. Over half (55%) of patients were on high dose (97/103 mg) Sacubitril/Valsartan. Primary outcome which was change in LVEF over the treatment period increased significantly following treatment with Sacubitril/ Valsartan from 25.33% at baseline to 30.14% at follow-up (p<0.001). There was no significant change in mean LVEF over a median duration of 11 months between prebaseline and baseline time points prior to

treatment. Mean increase in ejection fraction tended to be marginally greater in the medium/ high dose cohort as compared to the low dose cohort, with a mean increase of 5.09% (±1.36) and 4.03% (±3.17), respectively (p=0.184). Significant improvements were noted in left ventricular remodeling parameters including reductions in left ventricular end systolic diameter (LVESD) (3.36±1.6 mm), left ventricular end diastolic diameter (LVEDD) (2.64±1.1mm), and LV mass index (14.4±3.9 g/m2), (all *p* values <.05). There were also non statistically significant reductions in left ventricular end systolic volume (LVESV) and left ventricular end diastolic volume (LVEDV). All Sacubitril/Valsartan patients were optimized on OMT for a minimum of 1 yr prior to initiating Sacubitril/ Valsartan which suggests that improvements seen in EF are likely attributable to Sacubitril/Valsartan. Hence, Sacubitril/Valsartan was found to improve LVEF and multiple measures of reverse remodeling above and beyond the effect of pre-existing OMT.A trend towards greater improvement in LVEF was observed for patients treated with higher doses of Sacubitril/Valsartan.[29]

Although the long-term benefits of LCZ696 on cardiac function and prognosis have been explained, but effect of sacubitril/valsartan on cardiac dysfunction in the short-term remained to be elucidated. **Masanobu Ishii et al** conducted a study in year 2017 with aim to determine the effects of LCZ696 on acute phase of experimental myocardial infarction in mice, and to clarify whether LCZ696 has the cardioprotective effects beyond the RAAS blockade by comparison with enalapril. In this study, Wild-type mice subjected to ligation of left anterior descending artery were randomly allocated to 3 treatment groups 1 day after MI: LCZ696 (20 mg/kg BW/day), enalapril (4 mg/kg BW/day), and vehicle (corn oil only) groups. The LCZ696 group had was significantly higher survival rate with significantly lower rate of death due to LV rupture compared with the vehicle($p < 0.01$) and enalapril ($p < 0.05$) groups. The %FS was significantly improved 14 days and 28 days after MI in the LCZ696 group compared with the vehicle group ($p < 0.05$, mean

difference; 4.60, 95% confidence interval: 0.03 to 9.18, and p < 0.05,mean difference; 5.45, 95% confidence interval: 0.78 to 10.10, respectively), and tended to improve compared with enalapril. To investigate the mechanism of suppression of cardiac rupture by LCZ696, the mRNA expression levels of cytokines involved in cardiac inflammation and fibrosis were measured in the infarcted region 3 days after MI. The proinflammatory cytokines interleukin (IL)-1b, IL-6 mRNA expression was significantly lower in LCZ696 compared to the vehicle and enalapril groups. Matrix metalloproteinase-9 (MMP-9) mRNA expression which degrades extracellular matrix and is involved in remodeling, and development of cardiac rupture after MI was significantly lower in the infarcted region of LCZ696-treated mice compared to the vehicle (p=0.015) and enalapril (p=0.003) groups. Further, plasma biomarkers such as aldosterone levels were significantly lower in the LCZ696 group compared to the vehicle (p=0.014) and cyclic guanosine monophosphate (cGMP) levels, which is second messenger of natriuretic peptides, were significantly higher in the LCZ696 than the enalapril (p < 0.001), and vehicle (p= 0.033) groups The study showed that LCZ696 can prevent cardiac rupture after MI, probably due to the suppression of pro-inflammatory cytokines, matrix metalloproteinase-9 activity and aldosterone production, and enhancement of natriuretic peptides in mice. These findings suggest the mechanistic insight of cardioprotective effects of LCZ696 against acute MI, resulting in the belief that LCZ696 might be useful clinically to improve survival after acute MI.[30]

H Nazzari et al conducted a study in year 2017 to assess impact of sacubitril/valsartan on LV remodeling and functional status. Total of 129 HfrEF patients were switched to sacubitril-valsartan during study period. Of those, 43 patients had pre- and postechocardiograms with an average age of 58.0±12.9years. The average startingand attained doses on sacubitril-valsartan were 89.5 mg BID and 192.4 mg BID, respectively. The median time from LV assessment to initiation of sacubitril/valsartan was 177 days, whereas the median time from initiation of sacubitril/

valsartan to LV reassessment was 161 days. Average LVEF increased from 27.4±6.9% to 36.4±12.4%, p < 0.001), whereas LV end-diastolic dimension decreased from 67.6 mm to 65.2 mm (p= 0.01). There was no significant change in NYHA class post initiation of sacubitril/valsartan. It was concluded that switching from ACEI/ARB to sacubitril-valsartan in heart failure patients with reduced LVEF resulted in a significant increase in LVEF of almost 9%.These results suggested that sacubitril/valsartan is associated with reverse left-ventricular remodeling.[31]

Maurin V in year 2017 reported 129 consecutive systolic HF patients, treated with sacubitril/valsartan between October 2015 and July 2016, studied with serial echocardiographic examinations acquired before and after 3 months of treatment. Mean age was 59 years old, 76 % of patients were men, 52% had ischemic HF, and median duration of HF was 9, 6 years. All patients were in stable hemodynamic condition with an optimized medical treatment at baseline. Patients exhibited a significant reduction in left ventricular dimensions and volume (LVED diameter: 64.8 ± 10.9 vs 67.2 ± 8.6, p=0.003, LVED volume: 204.1 ± 79.3 vs 218.8 ± 79.1 mL, p <0.001, LVES volume:142.7± 70.1 mL vs158.9 ± 68.0 mL, p <0.001) with significant improvement in ejection fraction (31.9±8.2% vs 28.4±7.7 %, p <0.0011). Diastolic function improved significantly, left atrial volume was significantly smaller and systolic pulmonary pressures decreased significantly from 42.5±12.3 to 38.8±12.0 mmHg, p = 0.012. However, no significant change was observed in mitral regurgitation grade and right ventricular dimensions or function. It was concluded that Sacubitril/valsartan induces early reverse remodeling and improves pressure conditions in stable and well treated HFrEF patients.[32]

Groba-Marco M et al in year 2017conducted a retrospective study to analyse the evolution of left ventricle ejection fraction and end diastolic diameter in 17 patients with stable symptomatic HFrEF and optimized treatment after sacubitril/valsartan. Follow up transthoracic echocardiography was performed after mean time of 4.91±3.05 months

of treatment with ARNI. Mean LVEF before and after sacubitril/valsartan was 30±7.9% and 35.47 ± 10.3% respectively, with mean improvement 5.47±9.5% (p value = 0,031). Mean LVEDD before and after sacubitril/valsartan was 66.42±6.74mm and 62,42±7,5mm respectively, with mean reduction 4±5.3mm (pvalue = 0.025) Hence, a statistically significant improvement in LVEF and LVEDD was observed in patients with sacubitril/valsartan and optimal heart failure treatment.[33]

MerceFaraudo et al in year 2017 conducted a study on 30 chronic HF patients to analyse the impact of Sacubitril/Valsartan on functional capacity.6 minute walk test (6MWT) was performed before starting the treatment and after three months of having optimized the dose. Mean LVEF was 30%, with ischemic etiology in 37% pts, mean maximal tolerated dose was 98mg/day. 6 minute walk test improved from mean of 274±96 at baseline to 335±100 (p=0.05) after 3 months of treatment.[34]

In order to document the safety and consequences of transition from ACEI/angiotensin-II receptor blocker to Sacubitril/Valsartan, **Katerina Hlavata et al** in year 2017 conducted a study in 12 chronic stable HF outpatients with mean LVEF of 26.5%. Patients were converted from ACEI/ARB to SacubitrilValsartan. Laboratory evaluation, Minnesota Living with Heart Failure Questionnaire (MLHFQ), 6MWT was performed before the conversion and at 3-month follow-up visit. Conversion from ACEI/ARB to sacubitril/valsartan was not associated with any adverse events. At follow-up, patients improved in 6-min walk test by 55 m. It was concluded that transition from ACEI/ARB to sacubitril/valsartan therapy appears to be safe and leads to an improvement in exercise tolerance and quality of life.[35]

R. De Vecchis et al in year 2018 conducted a retrospective cohort study with aim to investigate the pharmaco-epidemiological aspects of sacubitril/valsartan. Sacubitril/valsartan was administered in addition to a beta-blocker and mineral receptor antagonist in a group of HFREF patients with NYHA class II-III HF vs. conventional therapy (ACE inhibitor or angiotensin II receptor blocker added to a beta-blocker plus an MRA)

administered to a control group of HFREF patients with comparable clinical features. In both groups, treatment was supplemented by a loop diuretic, usually furosemide, at variable doses. Patients assigned to therapy with sacubitril/valsartan had history of previous use of renin–angiotensin–aldosterone system inhibitors maintained for at least 3 months. Up-titration of sacubitril/valsartan was carried out at 2 weekly intervals to target dose of 97 + 103mg of sacubitril/valsartan to be given twice daily. The primary outcomes were all-cause death and HF hospitalizations. Safety outcomes were symptomatic hypotension, angioedema, hyperkalemia, and worsening renal function. The mortality rate for patients undergoing therapy with sacubitril/valsartan was 6.8% versus 34% in those undergoing conventional therapy (OR = 0.14; 95% CI = 0.04–0.49).HF hospitalizations in the observation period were 4.5% in the sacubitril/ valsartan group versus 59% in the conventional therapy group (OR = 0.03; 95% CI = 0.01–0.14). Need to increase the diuretic dose in the sacubitril/valsartan group was less frequent 9% versus 56.8% (OR = 0.08; 95% CI = 0.03–0.23). Safety outcomes included in the study showed a comparable profile in the two groups, with evidence of good tolerability of sacubitril/valsartan, except for the side effect of hypotension found in 15.9% of patients on sacubitril/valsartan versus 5.7% in the controls. It was concluded that Sacubitril/valsartan offered strong protection against all-cause death and HF hospitalizations at 6 months without any significant side effects.[36]

Patients with acute decompensated heart failure, which was defined by the presence of signs and symptoms that may lead to the use of intravenous therapy, were excluded from the PARADIGM-HF trial whose results were limited to ambulatory outpatients who had received established high highest doses of enalapril and sacubitril–valsartan during sequential single-blind run-in periods before randomization. **Eric J. Velazquez, M.D., et al in year 2018** conducted PIONEER-HF trial which

was designed to assess the efficacy and safety of the initiation of sacubitril/valsartan therapy, as compared with enalapril therapy, after hemodynamic stabilization among patients who were hospitalized for acute decompensated heart failure. The primary efficacy outcome was the time-averaged proportional change in the NT-proBNP concentration from baseline through weeks 4 and 8.Key safety outcomes were the incidences of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema. Time-averaged reduction in the NT-proBNP concentration was significantly greater in the sacubitril–valsartan group than in the enalapril group; the ratio of the geometric mean of values obtained at weeks 4 and 8 to the baseline value was 0.53 in the sacubitril–valsartan group as compared with 0.75 in the enalapril group (percent change, −46.7% vs. −25.3%; ratio of change with sacubitril/valsartan vs. enalapril 0.71; 95% confidence interval [CI], 0.63 to 0.81;P<0.001). Rates of worsening renal function, hyperkalemia, and symptomatic hypotension did not differ significantly between the sacubitril/valsartan group and the enalapril group.[37]

Raquel Rodil Fraile et al in year 2018 conducted an observational study to analyse the improvement of functional class and 6MWT in patients with advanced heart failure with reduced ejection function with sacubitril/ valsartan. Mean treatment time was 286 days. There was a significant difference of 55.68 m in the 6MWT after initiating sacubitril/valsartan (223.44 vs. 279.12, *P* <0.001). Seventy-four percent patients had New York Heart Association Functional Class IV initially. After the treatment, 91% presented an improvement in the NYHA functional class, with most patients in NYHA II and III class (51% and 40%, *P* = 0.002).[38]

S Kalantari et alin year 2018 performed prospective, single arm longitudinal study on 40 patients who were on optimal guideline directed medical therapy and were initiated on sacubitril/valsartan after an appropriate washout period from prior ACEI or ARB therapy. The primary

End point was the degree of reverse remodeling (change in LV and RV size, volume, shape, and function) as assessed by 2D and 3D transthoracic echocardiography at 3 months compared to baseline. Secondary endpoints were peak oxygen consumption (VO2), 6minute walk distance, and quality of life parameters. There was significant reduction in left ventricular and left atrial volumes with an increase in left ventricular ejection fraction as well as improvement in LV conicity index at 3 months. Mean LVEF improved from 32±7 to 35±7 ($p<0.01$), LVEDD and LVESD decreased from 6.2±0.8 cm to 6±0.8 ($p<0.01$) and 5.3±0.9 to 4.9±1($p<0.01$) respectively. Interim analysis revealed improved 6minute walk distance (428 ± 105 vs 451 ± 115 m; $p = 0.006$) and a trend towards improvement in peak oxygen consumption (VO2) (18.5 ± 5.7 vs 19.2 ± 5.6; $p = 0.19$) at 3 months. It was concluded that compared to a background of historical guideline directed medical therapy, transition to sacubitril/valsartan led to significant reverse remodeling and improved functional status.[39]

De Diego C in year 2018 conducted a study to evaluate the impact of ARNI as compared to angiotensin inhibition in LVEF and left ventricular diastolic size (LVDD). 250 HFrEF patients with 9 months of OMT with angiotensin inhibition (ACEI/ARB), beta blockers and mineralocorticoid antagonists were prospectively analyzed. Then, ACEI or ARB was changed to ARNI, which was tolerated for 9 additional months. After 3 months of ACEI/ARB, there was an initial increase of LVEF, maintaining constant values along time from 3-9 months. Then ARNI was started and a further significant increase of LVEF was observed. Under angiotensin inhibition, the LVDD remained stable. After ARNI, there was a significant decrease of LVDD. After 9 months with ACEI, patients averaged a LVDD of 62 ± 6 mm and LVEF of 31 ± 6% (80% ischemic) with NYHA of 2.4 ± -0.4. After 9 months with ARNI, NYHA improved to 1.5 ± 0.7 ($p<0.0002$), LVDD decreased (60 ± 6 mm, $p<0.02$) and LVEF increased (36.5 ± 8%, $p<0.002$). It was concluded that in a mainly ischemic HFrEF population,

Angiotensin neprilysin inhibition as compared to angiotensin inhibition further reversed cardiac remodeling leading an increase of LVEF, a predictor of sudden cardiac death.[40]

Martens et al in year 2018 performed a single-center, prospective study to determine the effect of sacubitril/valsartan therapy on cardiac structure in one hundred twenty five HFrEF patients previously treated with a maximum tolerated dose of ACE-I or ARB. The amount of RAS-blocker before and after switch to sacubitril/ valsartan was similar, indicating individual optimal dosing of sacubitril/valsartan. Over a median follow-up of 118 days after initiation of sacubitril/ valsartan, LVEF improved (29.6 ± 6% vs 34.8 ± 6%; *P* < .001) and Left ventricular end-systolic (147 ± 57 mL vs 129 ± 55 mL,*P* < .001) and end-diastolic volume (206 ± 71 mL vs197 ± 72 mL,*P* = .027) decreased. Volumetric remodeling was associated with a reduction in the degree of mitral regurgitation (1.59 ± 1.0 vs 1.11 ± 0.8; *P* < .001). Metrics of diastolic function improved; including a drop in the E/A-wave ratio (1.75 ± 1.13 vs 1.38 ± 0.88; *P* = .002). A dose-dependent effect was noted for changes in LVEF and LVESV with higher doses of sacubitril/valsartan leading to more reverse remodeling. This study concluded that In heart failure patients with reduced ejection fraction on optimal medical therapy who remain symptomatic, switching from an ACEI or ARB to sacubitril/valsartan induces beneficial cardiac reverse remodeling.[41]

Reduction in NT-proBNP during guideline directed medical therapy (GDMT) for HFrEF is associated with reverse LV remodeling, [42] however, no such link has been established for ARNI therapy. **James L. JanuzziJr et al in 2019** examined the association of the change in NT-proBNP after initiation of sacubitril-valsartan in patients with HFrEF with long-term changes in measures of cardiac remodeling. 654 patients completed the study. The median NT-proBNP concentration at baseline was 816 pg/mL and 455 pg/mL at 12 months (*P* < .001). At 12 months, LVEF increased from 28.2% to 37.8% (*P* < .001), while LVED volume index decreased

from 86.93 to 74.15 mL/m^2 (*P* < .001) and LVES volume index decreased from 61.68 to 45.46 mL/m^2 (*P* < .001). LA volume index and E/e′ ratio also decreased significantly. At 12 months, reduction in NT-proBNP concentration significantly correlated with improvement in markers of cardiac volume and function at 12 months. The observed reverse cardiac remodeling provided a mechanistic explanation for the effects of sacubitril-valsartan in patients with HFrEF.[43]

Geoffrey Bayard et al in year 2019 enrolled 52 HFrEF patients, hospitalized for HF within the previous 12 months to study the impact of sacubitril/valsartan on LV remodeling. Echo evaluation was performed before initiating sacubitril/valsartan and 3 months after optimal dose adjustment. Several echo parameters significantly improved with LVEF improving from 32.6± 5 to 36 ± 6% (p= 0.0001); LV end systolic volume from 117 ± 40 to 108 ± 46 mL (p = 0.0051); LV end diastolic diameter from 60±4 to 57±5mm(p=0.0002); mean right ventricular systolic pressurefrom39±10 to 32±8 (p=0.0001). No significant modifications were observed concerning LV diastolic parameters or RV echo parameters. Sacubitril/valsartan echo responders had less severe LV remodeling as compared to non responders. This study concluded that in HFrEF patients, sacubitril/valsartan significantly improves LV systolic remodelling, without any significant effect on LV diastolic or RV systolic echo parameters. Sacubitril/valsartan responders exhibit both less severe LV remodelling and less significant mitral regurgitation. Hence, sacubitril/valsartan could be used as soon as possible in HFrEF patients in order to limit LV remodelling, while precluding non-response or intolerance.[44]

Yiwen Wang et al in year 2019 conducted a meta analysis to compare the effects of ARNI versus angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on cardiac reverse remodeling (CRR)

Indices. Databases for studies published between 2010 and 2019 that reported CRR indices following ARNI administration were searched. Effect size was expressed as mean difference (MD) with 95% CIs. Twenty studies enrolling 10,175 patients were included. ARNI improved functional capacity in patients with heart failure (HF) and reduced ejection fraction (EF), including increasing New York Heart Association functional class (MD 0.79, 95% CI 0.86-0.71) and 6-minute walking distance (MD 27.62 m, 95% CI 15.76 - 39.48). ARNI outperformed angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers in terms of CRR indices, with striking changes in left ventricular EF, diameter, and volume. Significant increment in LVEF (MD 4.89%, 95% CI 4.13- 5.65) among HFrEF subjects was noted. Mean LVESV decreased by 18.23 mL compared with baseline after treatment with ARNI (95% CI, 27.25- 9.20), and mean LVEDV decreased by 21.60 mL (95% CI, 24.32-18.88) in HFrEF patients. Likewise, LVESD (MD-3.50 mm, 95% CI, 5.56-1.44;), LVEDD (MD-2.42 mm, 95% CI, 3.06-1.78;), LA volume (MD-7.59 mL, 95% CI, 14.03-1.14;), were all significantly reduced in patients with HFrEF. Improvements in CRR indices were observed at 3 months and became more significant with longer follow-up to 12 months.[45]

Adverse LV remodeling after myocardial injury causes tethering of mitral valve preventing sufficient coaptation of normal leaflets and resulting in functional mitral regurgitation Although beta blockers, angiotensin-converting-enzyme inhibitors, and angiotensin receptor blockers could partially attenuate LV dilatation and remodeling after myocardial injury, their effects on LV remodeling were insufficient for reducing the severity of MR and the morbidity and mortality of patients with functional MR remain high despite standard medical therapy .[46] ***Kang & Park et al*** conducted a study in year 2019 to assess the therapeutic impact of ARNI on functional MR. Hypothesis of this study was that sacubitril/valsartan would be superior to valsartan alone in improving functional MR via dual inhibition of the renin-angiotensin system and neprilysin. 118 heart failure patients with

chronic functional MR secondary to left ventricular dysfunction were assigned to receive either sacubitril/valsartan or valsartan, in addition to standard medical therapy for heart failure. The primary end point was the change in effective regurgitant orifice area (EROA) of functional MR from baseline to the 12-month follow-up. Secondary end points included changes in regurgitant volume, LV end-systolic volume, LV end-diastolic volume and incomplete mitral leaflet closure area Cause of functional MR was ischemic in 36% patients and non-ischemic in 64%. Mean LVEF was 34±7%, mean EROA of MR was 0.20±0.10 cm2, and mean regurgitant volume was 35±16 ml. Decrease in EROA was significantly greater in the sacubitril/valsartan group compared to the valsartan group (-0.058±0.095 versus -0.018±0.105 cm2; P=0.032). Regurgitant volume was also significantly decreased in the sacubitril/valsartan group compared with the valsartan group (mean difference -7.3 ml, 95% CI -12.6 to -1.9; P=0.009). There were no significant between group differences regarding the changes in incomplete mitral leaflet closure area and LV volumes except LV end-diastolic volume index (P=0.044).It was concluded that among patients with secondary functional MR, sacubitril/valsartan reduced MR to a greater extent than did valsartan. The findings suggest that an angiotensin receptor neprilysin inhibitor might be considered for optimal medical therapy of patients with heart failure and functional MR.[47] **Matteolandolfo et al in year 2020** assessed SV impact on clinical and echocardiographic parameters in HFrEF outpatients previously treated with optimized therapy. Results were also stratified by sex to analyse possible sex-based differences in reverse remodelling response to sacubitril/valsartan. Forty-nine HFrEF outpatients were retrospectively included in the study. Data was collected from transthoracic echocardiography and clinical assessment at baseline and after 3 ± 1 and 12 ± 1 months of treatment with sacubitril/valsartan. After 3 months of treatment significative improvement of both systolic and diastolic function with a reduction of left ventricular mass and relative wall thickness was

observed. At 12 months, a further improvement of all previous parameters, plus systolic pulmonary artery pressure (PASP) and left atrial diameter was observed. In women, most of the echocardiographic parameters improved after sacubitril/valsartan initiation, but did not reach the statistical significance, except for left ventricular ejection fraction, PASP and LA diameter. As for clinical parameters, sacubitril valsartan improved New York Heart Association Class, systolic blood pressure and loop diuretic dosage with a mild but significative increase in serum creatinine and potassium. Hence, significant reverse remodeling was observed with sacubitril valsartan with women showing a lesser extent of reverse remodelling compared with men.[48]

Li-Wei Liu et alin year2020demonstrated a significant improvement in LVEF 35 ± 6.1% to 50± 8.8% ($p < 0.001$) in a prospective, single armed, observation cohort study in patients with HFrEF after 6 months of sacubitril/valsartan therapy. Sacubitril/valsartan was prescribed as both first-line and second-line therapy to every eligible patient regardless of whether they were already on standard therapy or newly-diagnosed with HFrEF. LV end diastolic diameter decreased from 6.0±0.7 cm to 5.5±0.8 cm ($p < 0.001$), with similar findings in LV end systolic diameter and LA diameter. The average NT-proBNP level decreased from 6379 pg/mL to 1661 pg/dl. Patients were divided into two groups as those with or without ACEI and ARB pre-treatment. Both groups had similar improvements in ejection fraction and chamber size after using sacubitril/valsartan. Both the ICMP and DCMP groups showed significant improvements in LVEF compared to baseline LVEF. [49]

MATERIALS AND METHODS

Our study was a single centre study conducted at Hero DMC heart institute, Ludhiana from May 2019 to October 2020 that consisted of 100 patients with HFrEF patients who were already on ace inhibitors in addition to optimal medical therapy enrolled from DMC & HOSPITAL.

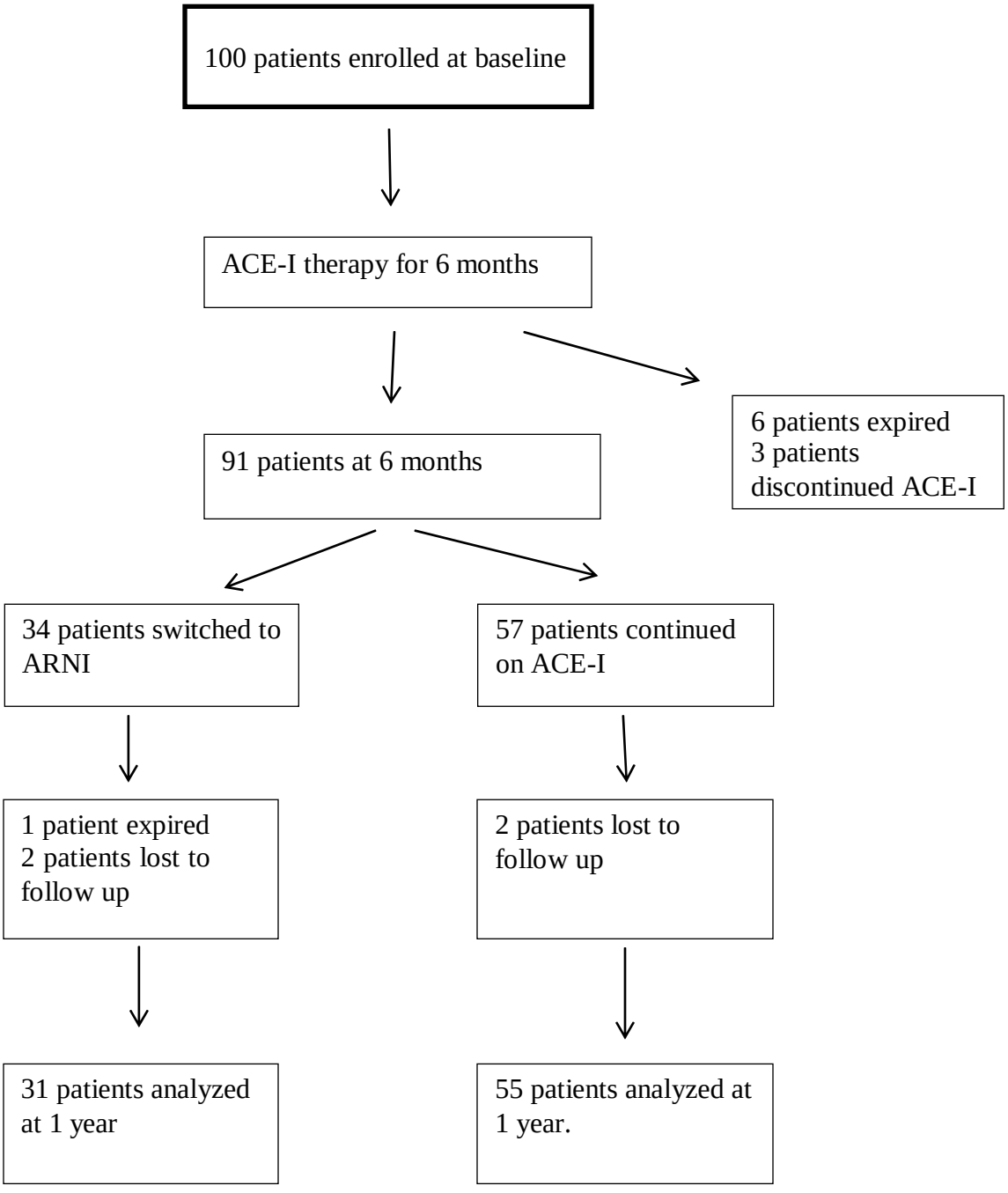
These patients were analysed at baseline by NYHA FUNCTIONAL CLASS, 6 minute walk test and transthoracic echocardiography(TTE). Imaging data was analysed for LV dimensions and volume.

These patients were followed up for six months and reassessed for NYHA class, 6 minute walk test and transthoracic echocardiography.

Thereafter, patients were given option for ARNI (sacubitril/valsartan therapy) and those who opted, were switched over from ace inhibitor to sacubitril/valasartan therapy on maximum tolerated dose after stopping ace inhibitors for 36 hours while remaining patients continued on ace-i therapy. All patients were followed up for additional 6 months and thereafter reassessed for NYHA class, 6 minute walk test and TTE.

At the completion of study (1 year), comparison was done between both groups (ACE-I and ARNI) for echocardiographic parameters and functional status at the time of division into two groups and after 6 months of therapy. Also, these parameters were compared at both time intervals in each group.

FIGURE 1: Flowchart of the study population


100 patients enrolled at baseline
ACE-I therapy for 6 months
6 patients expired
3 patients discontinued ACE-I
91 patients at 6 months
34 patients switched to ARNI
57 patients continued on ACE-I
1 patient expired
2 patients lost to follow up
2 patients lost to follow up
31 patients analyzed at 1 year
55 patients analyzed at 1 year.

As shown in above flowchart, 100 patients were recruited at baseline.

6 patients expired and 3 patients discontinued ACE-I due to dry cough during initial 6 months of follow up. Thereafter patients were given option for ARNI (sacubitril/valsartan therapy) and 34 patients were switched over from ace inhibitor to sacubitril/valasartan therapy after stopping ace inhibitors for 36 hours while 57 patients were continued on ACE-I therapy. These patients were followed up for additional 6 months during which period 2 patients were lost to follow up in each group and 1 patient expired in ARNI group. Final analysis at end of 1 year was done with 31 patients in ARNI group and 55 patients in ACE-I group.

The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent of heart failure.[50] It places patients in one of four categories based on how much they are limited during physical activity. The 6-min walk test (6 MWT) is a submaximal exercise test that entails measurement of distance walked over a span of 6 minutes. The 6 MWT provides information regarding functional capacity, response to therapy and prognosis across a broad range of chronic cardiopulmonary conditions.[51] 6 patients in our study were not able to perform 6 minute walk test because of orthopaedic disability.

TTE was used for measurement of LV dimensions and volume. The most commonly used 2D method for volume measurements is the biplane method of discs (modified Simpson‟s rule). [52] The principle underlying this method is that the total LV volume is calculated from the summation of a stack of elliptical disks. LV volumes are measured from apical 4 and/or apical 2 chamber views, tracing the endocardial border of the LV. If there is no wall motion abnormality, the LV ejection fraction (EF) can be estimated from one view only, apical 4 chambers or apical 2 chamber view. The ejection fraction is calculated from the difference between end-diastolic and end-systolic LV volume, divided by the end-diastolic LV volume.

$$EF = \frac{\text{End-diastolic volume - end-systolic volume}}{\text{End-diastolic volume}}$$

Apart from EF, other echocardiographic parameters compared in our study were LV internal diameter systole (LVIDs), LV internal diameter diastole (LVIDd), Left atrial (LA) diameter, Mitral valve E/A ratio, mitral regurgitation severity, pulmonary artery systolic pressure(PASP) and Tricuspid annular plane systolic excursion (TAPSE).

Inclusion Criteria:

Patients with HFrEF (EF<40%).

Exclusion Criteria:

1. Symptomatic hypotension (systolic blood pressure of less than 100 mm Hg)
2. An estimated glomerular filtration rate (eGFR) below 30 ml per minute per 1.73 m2 of body-surface area,
3. Serum potassium level of more than 5.0 mmol per liter.
4. History of angioedema or unacceptable side effects during receipt of ACE inhibitors or ARBs.

The study was approved by institutional ethics committee.

Statistical Analysis: After data had been collected, it was subjected to analysis using appropriate statistical methods. The data obtained at various stages of the study was compared taking into account the specific objectives of the study.

OBSERVATIONS AND RESULTS

Table 1: Baseline characteristics of patients

	Mean sd
Age (years) ± SD	60.07 ± 10.531
Male (n,%)	68(68%)
Female (n,%)	32(32%)
ICMP (n, %)	80(80%)
NICMP (n, %)	20(20%)
NYHA CLASS II (n,%)	33(33%)
NYHA CLASS III (n,%)	61(61%)
NYHA CLASS IV(n,%)	6(6%)
CREATININE(mg/dl) ± SD	0.92±0.28
SODIUM (meq/l) ± SD	136.48±3.73
POTASSIUM (meq/l) ± SD	4.20±0.43
BNP (pg/ml) ± SD	855.95± 905.75
6 minute walk distance (metres) ± SD	245.78± 94.84

Table 1 shows the baseline characteristics of 100 patients enrolled in the Study. The patient's age ranged from minimum of 36 years to maximum of 79 years with a mean of 60.07 years. There were 68 male cases while 32 were female out of 100.Pts with ischaemic cardiomyopathy constituted 80% of study population while 20% pts suffered from non-ischaemic cardiomyopathy. 33 pts were in NYHA class II, 61 pts in NYHA class III and 6 pts were in NYHA class IV at time of enrollment. Mean BNP at baseline was 855.95pg/ml (SD=905.75). Mean 6 minute walk distance of the pts was 245.78 metres (SD=94.84). Mean creatinine, sodium, potassium of patients was 0.92 (SD=0.28), 136.48 (SD=3.73) and 4.20(SD=0.43) respectively.

TABLE 2: Age distribution of study population

Age Group	No. of cases	Percentage
< 50	24	24.0%
51-60	24	24.0%
61-70	34	34.0%
>70	18	18.0%
Total	100	100.0%

As shown in the above table, patient's age ranged from minimum of 36 years to maximum of 79 years with a mean of 60.07 years. Maximum numbers of cases were seen in age group of 51-70 years constituting 58% of patients.

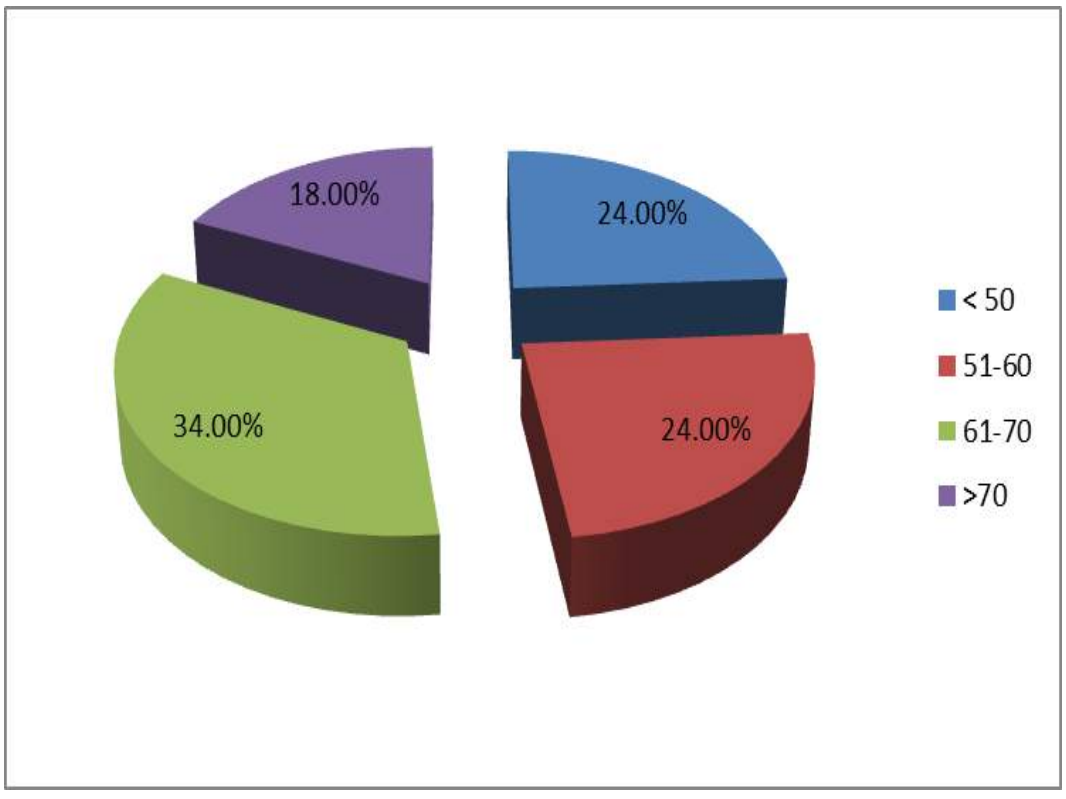


FIGURE 2: Age distribution of study population

TABLE 3: Distribution of comorbidties in study population

Past History	No. of cases	Percentage
DM	53	53.0%
HTN	37	37.0%
CVA	2	2.0%
THYROID	1	1.0%
AF	13	13.0%

As shown in above table, 53 patients were suffering from diabetes, 37 pts had hypertension, 2 pts had CVA, and 1 patient had thyroid disease. 13 pts had atrial fibrillation at baseline, 2 pts initially in sinus rythum had atrial fibrillation at 6 months and 1 pt developed AF at 1 year.

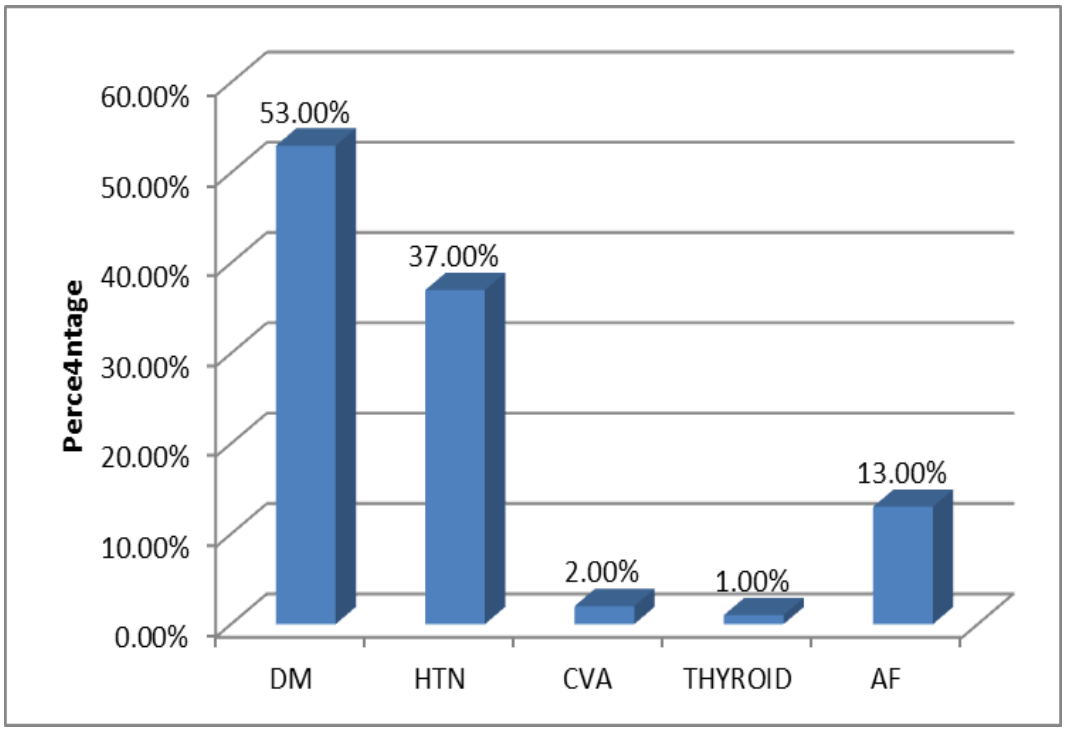


FIGURE 3: Distribution of comorbidities in study population

TABLE 4: Distribution of drugs among the cases enrolled

Baseline Therapy	No. of cases	Percentage
B Blockers	47	47.0%
ACE-I	100	100.0%
CCB	14	14.0%
MRA	45	45.0%
LOOP DIURETICS	100	100.0%
IVABRADINE	6	6.0%

As depicted in the above table, 100% patients were receiving ACE Inhibitors and diuretics. 47 patients (47%) were on beta blocker therapy, 45 patients (45%) were receiving mineralocorticoid receptor blockers, 14 pts (14%) were receiving calcium channel blockers and 6 pts (6%) were receiving ivabradine.

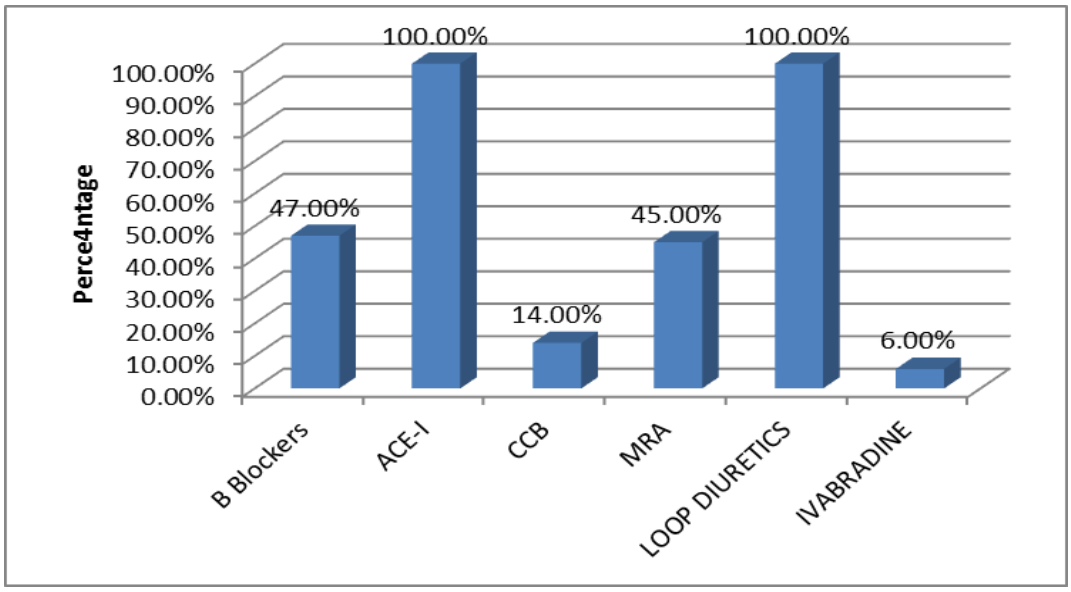


FIGURE 4: Distribution of drugs among the cases enrolled

TABLE 5: Baseline ECG changes among cases enrolled.

BASELINE ECG	No. of cases	Percentage
AF	11	11.0%
AF RBBB	2	2.0%
IVCD NSR	4	3.0%
LBBB NSR	6	6.0%
LAFB NSR	4	4.0%
NSR	69	70.0%
RBBB NSR	4	4.0%
Total	100	100.0%

As shown in above table, 13 patients had atrial fibrillation at time of enrollment, 4 pts had ivcd, 6 pts had LBBB, 4 pts had RBBB and 4 patients had left anterior fascicular block.

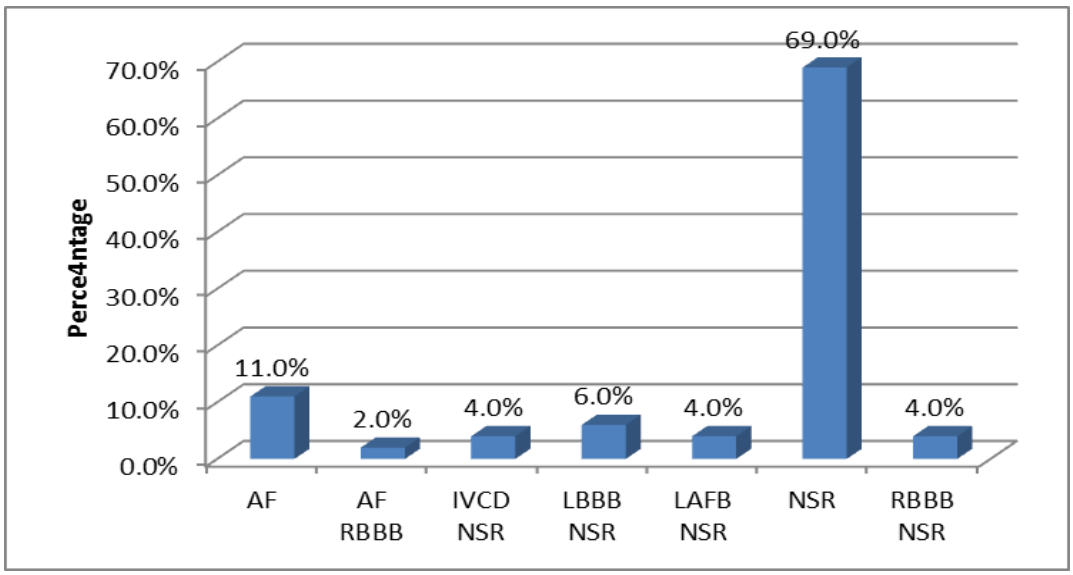


FIGURE 5: Baseline ECG changes among cases enrolled.

Table 6: Echocardiographic parameters of patients at baseline

	MEAN
LVEF(%)±SD	29.79±5.82
LVIDs(mm)±SD	50.55±9.39
LVIDd(mm) ±SD	61.57±11.33
LA Diameter(mm) ±SD	42.38±7.61
MV E/A ±SD	1.13±0.45
PASP(mm hg) ±SD	34.21±17.09
TAPSE(mm) ±SD	22.44±2.97
MR (n, %)	Mild mr- 30% (30%) Moderate mr- 36(36%) Severe mr- 13(13%)

The mean LV ejection fraction of pts was 29.75% (SD=5.82).The mean LV internal systolic diameter was 50.55 mm SD=9.39whereas mean LV internal diastolic diameter was 61.57 mm SD=11.33.The mean LA diameter of pts was 42.38mm SD=7.61 .Mean MV E/A ratio of patients was1.13 SD= 0.45. Pts enrolled had mean PASP of 34.21 SD= 17.09 and tapse of 22.44 SD=2.97.21% of pts had no mr, 30% had mild MR, 36% had moderate MR and 13% had severe MR.

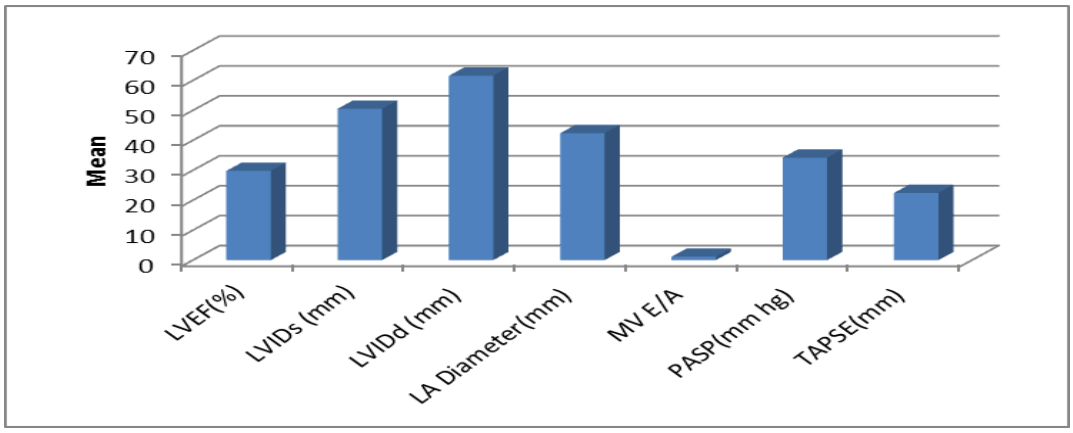


FIGURE 6: Echocardiographic parameters of patients at baseline

Table 7: Comparison of Clinical and Echocardiographic Parameters at Baseline and at 6 months.

	Baseline	6 month	T	p-value	Significance
	Mean±SD	Mean±SD			
6 MWD	249.72±96.29	258.18±79.22	-1.360	0.177	NS
EF	30.41±5.48	30.98±6.49	-1.135	0.259	NS
LVIDs	50.22±9.54	49.84±10.08	0 .599	0.551	NS
LVIDd	61.54±11.69	61.46±11.74	0.135	0.893	NS
LA	42.19±7.50	41.53±6.99	1.792	0.076	NS
MV E/A	1.13±0.46	1.15±0.44	-0.484	0.630	NS
PASP	32.98±16.43	30.89±13.50	1.507	0.135	NS
TAPSE	22.37±2.83	22.56±3.10	-0.986	0.327	NS

In our study, 100 patients enrolled in the study were followed up for 6 months. During this period patients remained on ACE-I therapy. Clinical and echocardiographic parameters were reassessed at 6 months and compared with parameters at baseline. As shown in above table, there was no significant difference observed in various parameters at baseline and at 6 months.

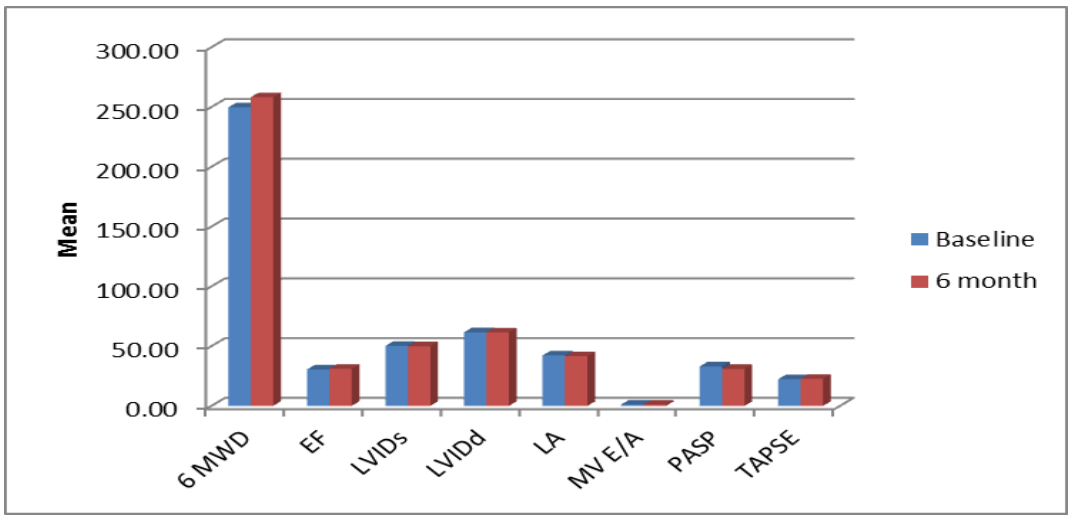


FIGURE 7: Comparison of Clinical and Echocardiographic Parameters at Baseline and at 6 months.

TABLE 8: Comparison of MR severity at baseline and at 6 months

	Baseline		6 month			
MR SEVERITY	No. of cases	Percentage	No. of cases	Percentage	McNemar-Bowker Test	p-value
MILD MR	30	30.0%	26	28.6%		
MOD MR	36	36.0%	33	36.3%		
SEVERE MR	13	13.0%	12	13.2%		0.607
NO MR	21	21.0%	20	22.0%		
Total	100	100.0%	91	100.0%	1.000	

In our study, pts were categorized according to severity of mitral regurgitation.30 pts had mild MR, 36 had mod MR, 13 pts had severe MR and 21 pt had no MR at baseline. At 6 months 26 pts were in mild MR, 33 in mod MR, 12 pts in severe MR, 20 pts in no MR category. No difference was obtained in patient distribution in various categories of MR.

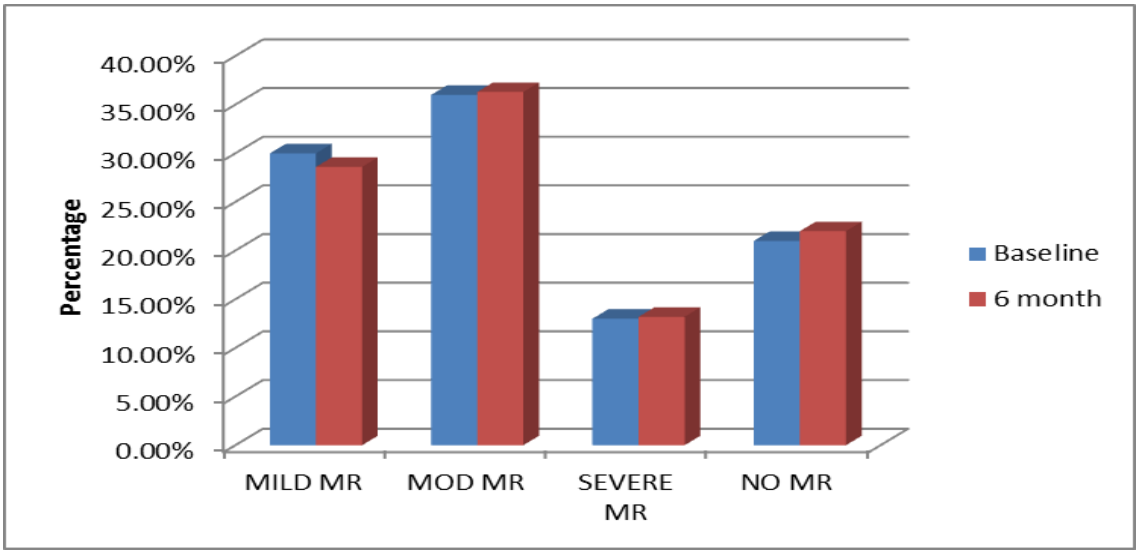


FIGURE 8: Comparison of MR severity at baseline and at 6 months

TABLE 9: Comparison of NYHA class at baseline and at 6 months

	Baseline		6 month	
NYHA CLASS	No. of cases	Percentage	No. of cases	Percentage
II	33	33.0%	43	47.3%
III	61	61.0%	48	52.7%
IV	6	6.0%	0	0.0%
Total	100	100.0%	91	100.0%

At baseline, 33 pts were in NYHA class II, 61 pts in NYHA class III and 6 pts in NYHA class IV. At 6 months 43 pts were in NYHA class II, 48 pts in NYHA class III and no pt was in NYHA class IV. 4 pts who were in NYHA class IV at baseline expired subsequently, 2 pts has improved NYHA class from IV to III.

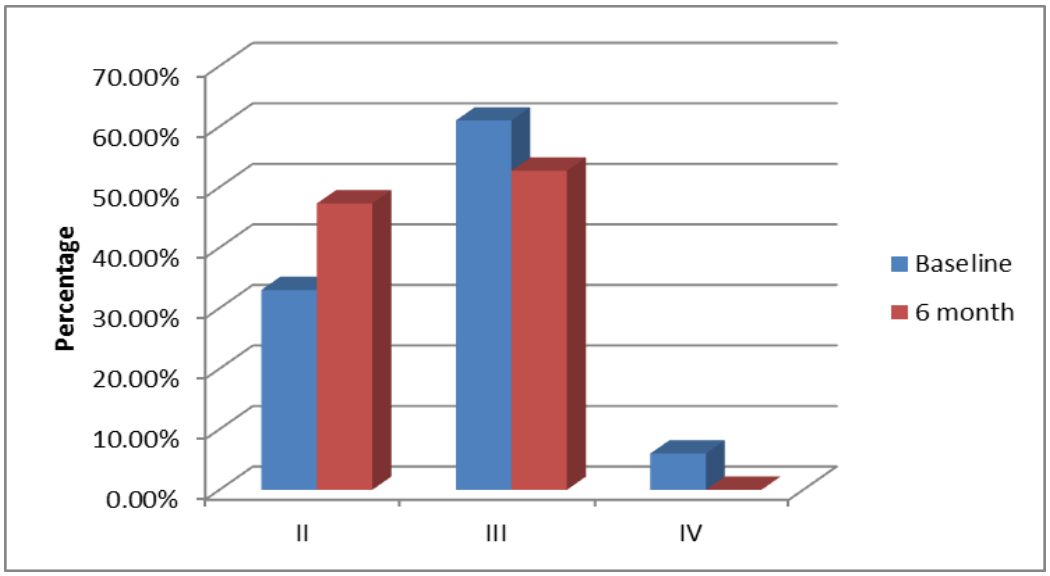


FIGURE 9: Comparison of NYHA class at baseline and at 6 months

TABLE 10: Comparison of mean age between ACE and ARNI Group.

	ACE-I GROUP Mean±SD	ARNI GROUP Mean±SD	T	P value	Significance
AGE	58.79±10.65	62.56±9.99	-1.713	0.090	NS

At 6 months of study, 34 patients were switched to ARNI whereas 57 patients continued on ACE-I therapy. Both the groups were followed up for 6 months thereafter and reassessed.

No significant difference was observed in mean age of both groups.

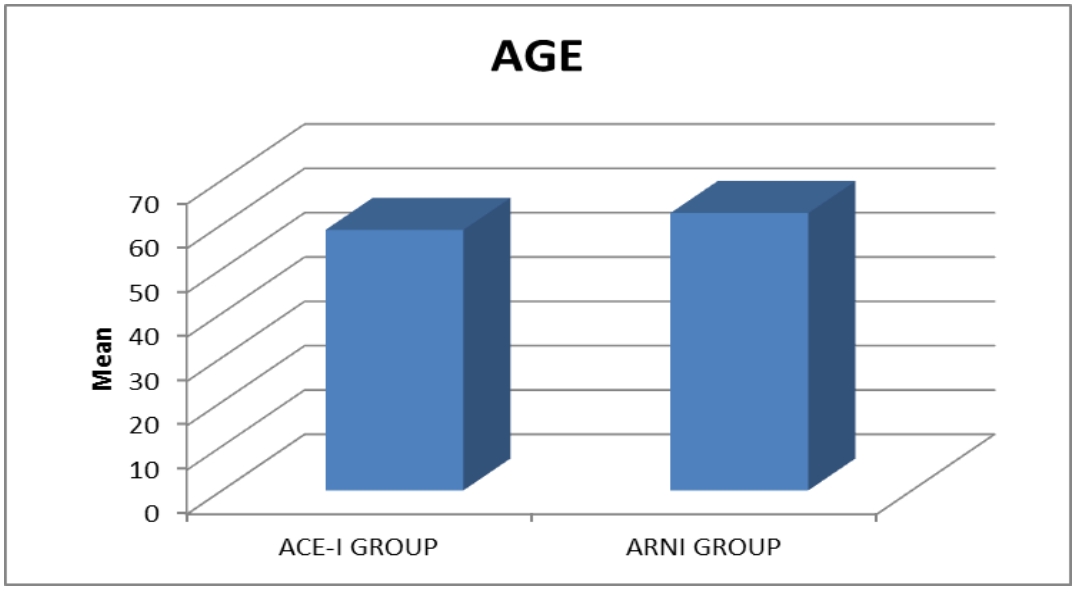


Figure 10: Comparison of mean age between ACE and ARNI Group.

TABLE 11: Comparison of baseline characteristics of patients in ACE-I and ARNI group

		ACE-I		ARNI		Chi square value	p-value
Sex	F	17	29.82%	9	26.47%	0.117	0.732
	M	40	70.18%	25	73.53%		
Etiology of Heart Failure	NICMP	10	17.54%	6	17.65%	1.781	0.411
	ICMP	47	82.46%	28	82.35%		
Comorbidities	DM	30	52.63%	18	52.94%	0.001	0.977
	HTN	19	33.33%	14	41.18%	0.567	0.452
	CVA	1	1.75%	1	2.94%	0.140	0.709
	Thyroid	1	1.75%	0	0.00%	0.603	0.437
	AF	7	12.28%	3	8.82%	0.260	0.610
Baseline Therapy	Beta Blockers	25	43.86%	20	58.82%	1.908	0.167
	MRA	26	45.61%	13	38.24%	0.473	0.491
	Ivabradine	4	7.02%	2	5.88%	0.045	0.833

As evident in above table, no difference was observed in various baseline characteristics in ACE-I and ARNI group. There was male predominance in both groups. Ischemic cardiomyopathy was the etiology of heart failure in 82.46% of pts in ACE-I group and 82.35% of pts in arni group. No difference was observed in prevalence of various comorbities such as diabetes, hypertension, atrial fibrillation, cva, thyroid disorders in both groups. 43.86% of pts in ACE-I group and 58.82% pts in ARNI group were receiving beta blockers whereas 45.61% in ACE-I group and 38.24% in ARNI group were receiving Mineralocorticoid receptor antagonists. All pts received loop diuretics. No difference was observed in various baseline therapies in both groups.

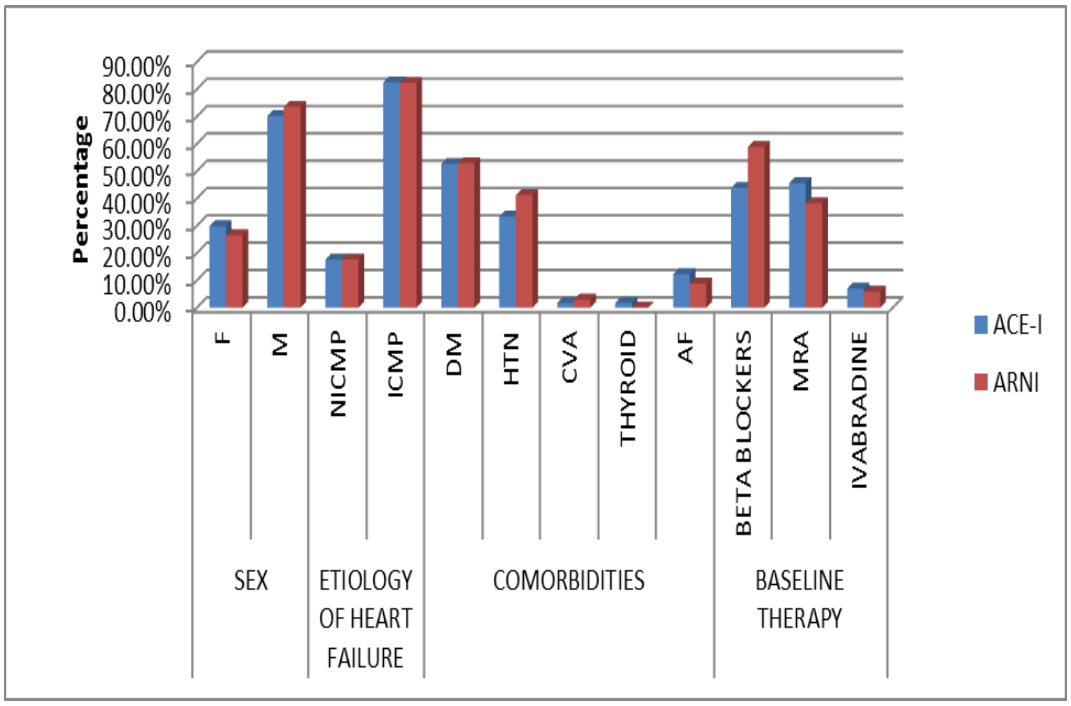


FIGURE 11: Comparison of baseline characteristics of patients in ACE-I and ARNI group

TABLE 12: Comparison Of Clinical and Echo parameters at 6 month Follow up in ACE-I Group.

ACE-I	6 month	12 month	T	p-value	Significance
	Mean± SD	Mean± SD			
6 MWD	252.08±86.51	258.65±87.27	-3.084	0.003	S
EF	31.35±7.19	31.44±7.28	-0.527	0.601	NS
LVIDs	49.64±10.61	49.29±10.48	1.343	0.185	NS
LVIDd	61.73±12.55	61.60±12.46	0.586	0.560	NS
LA	41.51±6.67	41.07±6.64	1.398	0.168	NS
MV E/A	1.19±0.43	1.21±0.40	-1.594	0.117	NS
PASP	30.69±14.82	28.15±12.87	3.369	0.001	S
TAPSE	22.73±3.05	22.78±3.07	-1.000	0.322	NS

As shown in above table, in ACE-I group, 6MWD increased from 252.08m (SD=86.51) to 258.65m (SD=87.27) after 6 months of ACE-I therapy. PA systolic pressures decreased by 2.55 mm at 6 month follow up (p=0.001). No significant difference was observed in EF, LV systolic and diastolic dimensions, LA size, MV E/A and RV function after ACE-I therapy.

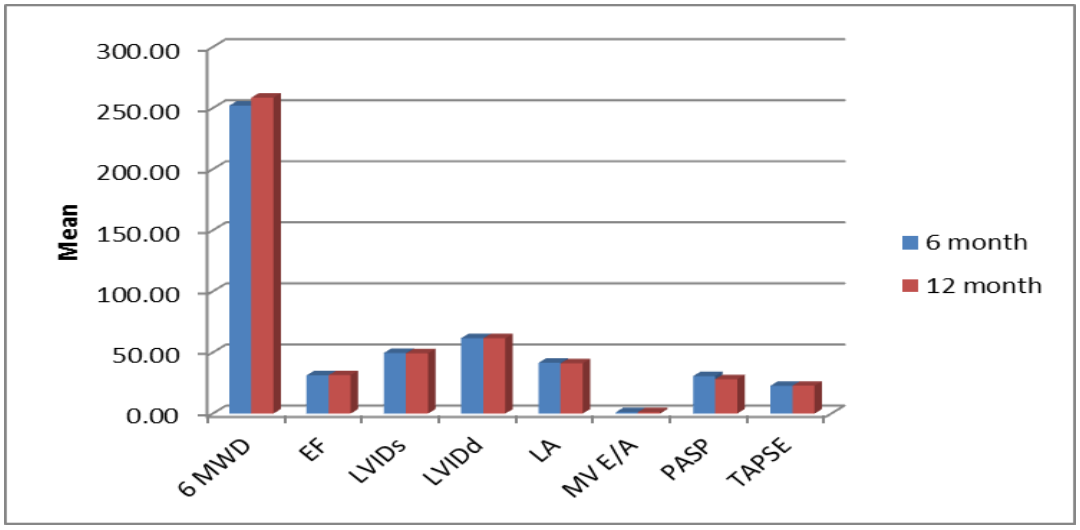


FIGURE 12: Comparison Of Clinical and Echo parameters at 6 month Follow up in ACE-I Group.

TABLE 13: Comparison Of Clinical and Echoparameters at 6 Month Follow up In ARNI Group.

ARNI	6 month	12 month	T	p-value	Significance
	Mean± SD	Mean± SD			
6 MWD	281.55±57.06	384.34±60.42	-9.932	0.000	S
EF	31.23±4.82	35.68±5.57	-5.698	0.000	S
LVIDs	49.26±8.53	44.77±9.03	5.800	0.000	S
LVIDd	60.55±10.13	57.45±10.11	5.101	0.000	S
LA	41.35±7.71	38.55±6.69	3.871	0.001	S
MV E/A	1.00±0.37	1.10±0.26	-1.684	0.104	NS
PASP	31.06±10.87	27.48±9.22	2.599	0.014	S
TAPSE	22.74±3.12	22.77±3.20	-0.138	0.891	NS

After 6 months of ARNI therapy, 6MWD increased significantly from 281.55m (SD=57.06) to384.34m (SD=60.42).EF increased by 4.45% from 31.23% (SD=4.82) to 35.68% (SD=4.82), (p=0.000). LV systolic and diastolic diameters decreased significantly by 4.48 mm and 3.10 mm respectively. Significant reduction of 2.81 mm was seen in La size. No significant difference was observed in MV E/A ratio or TAPSE after ARNI therapy. Significant reduction of 3.58 mm was recorded in PA systolic pressures at 6 months of follow up with ARNI therapy.

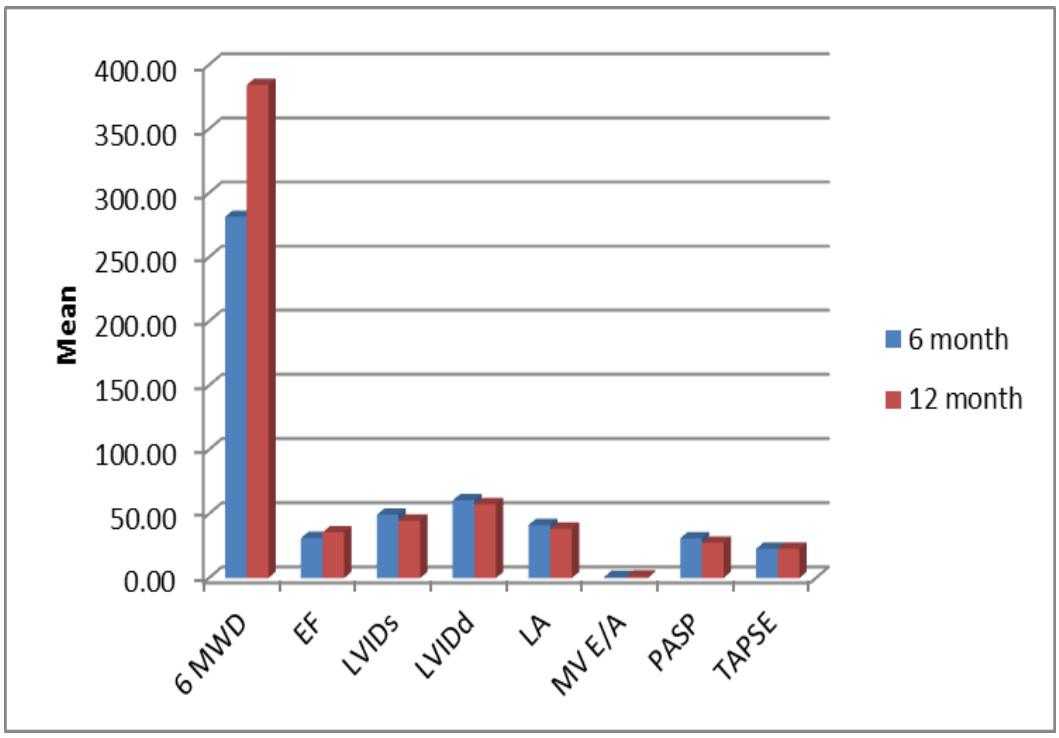


FIGURE 13: Comparison Of Clinical and Echo parameters at 6 Month Follow up In ARNI Group.

TABLE 14: Comparison of 6 minute walk distance between ACE-I AND ARNI Group at 6 month follow up.

	ACE-I	ARNI			
	Mean±SD	Mean±SD	T	p-value	Significance
6MWD (6Months)	250.94±85.06	270.16±68.04	-1.085	0.281	NS
6MWD (12Months)	258.65±87.27	384.34±60.42	-6.868	0.000	S
6 MWD (6-12 diff)	6.57±15.21	102.79±55.74	- 11.639	0.000	S

6MWD was 250.94 metres (SD=85.06) in ACE-I and 270.16(SD=68.04) in ARNI group at time of randomization with no significant difference observed in both groups. After 6 months of therapy, 6MWD increased by 6.57 m (SD=15.21) in ACE-I group and 102.79 metres (SD=55.75) in ARNI group (p value=0.000).Hence, 6MWD significantly improved with 6 months of ARNI therapy as compared to ACE-I therapy.

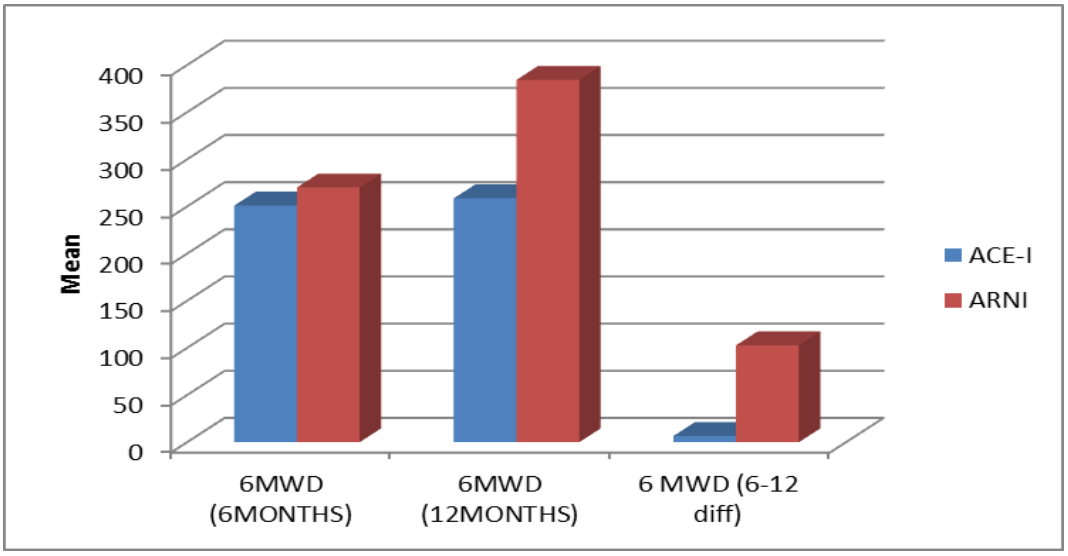


FIGURE 14: Comparison of 6 minute walk distance between ACE-I AND ARNI Group at 6 month follow up.

TABLE 15: Comparison of Ejection fraction between ACE-I and ARNI Group at 6 months follow up.

	ACE-I	ARNI			
	Mean± SD	Mean± SD	T	p-value	Significance
EF (6 Months)	31.33±7.07	30.38±5.45	0.674	0.502	NS
EF(1Year)	31.44±7.28	35.68±5.57	-2.810	0.006	S
EF (6-12 diff)	-0.09±1.28	-4.45±4.35	6.947	0.000	S

As shown in above table, after 6 months of therapy, EF increased by 0.09% (SD=1.28) in ACE-I group and 4.45 %(SD=4.35) in ARNI group with difference reaching statistical significance(p value=0.000).

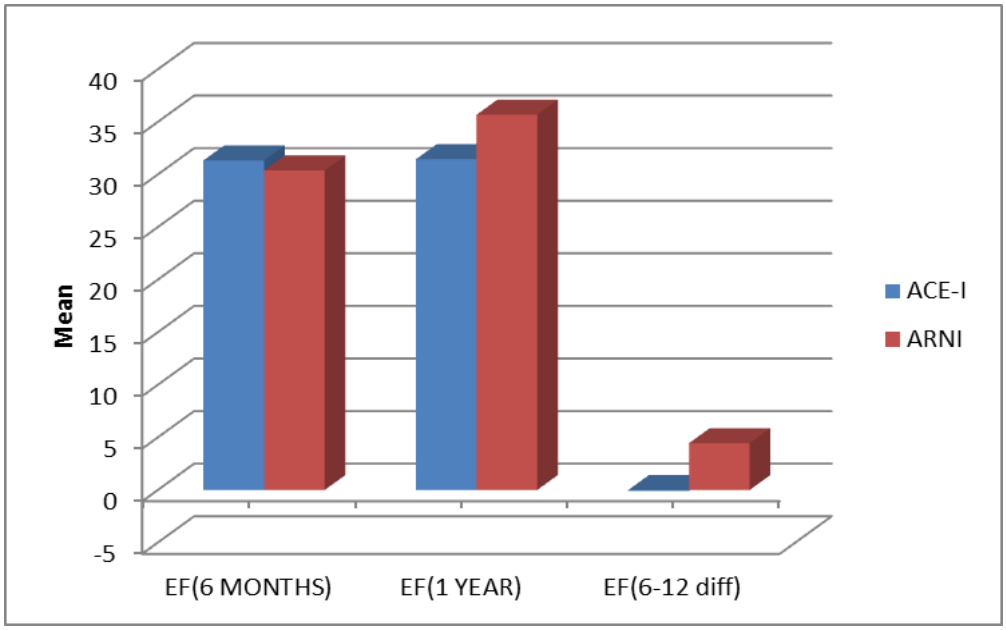


FIGURE 15: Comparison of Ejection fraction between ACE-I and ARNI group at 6 months follow up

TABLE 16: Comparison of LV internal systolic diameter between ACE-I and ARNI group at 6 months follow up.

	ACE-I	ARNI			
	Mean± SD	Mean± SD	T	p-value	Significance
LVIDs (6 Months)	49.56±10.55	50.29±9.37	-0.334	0.739	NS
LVIDs (1 Year)	49.29±10.48	44.77±9.03	2.013	0.047	NS
LVIDs (6-12 diff)	0.35±1.91	4.48±4.30	-6.158	0.000	S

At shown in above table, after 6 months of therapy, LV internal systolic diameter decreased by 0.35mm (SD=1.91) in ACE-I group and 4.48 mm (SD=4.30) in ARNI group with difference reaching statistical significance (p=0.000).

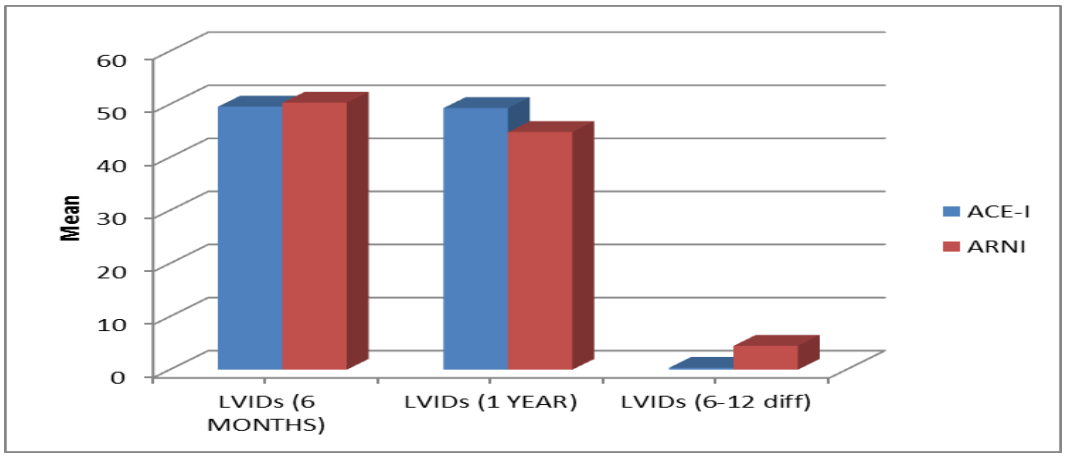


FIGURE 16: Comparison of LV internal systolic diameter between ACE-I and ARNI group at 6 months follow up.

TABLE 17: Comparison of LV internal diastolic diameter between ACE-I and ARNI group at 6 month follow up

	ACE-I	ARNI			
	Mean± SD	Mean± SD	T	p-value	Significance
LVIDd (6 Months)	61.73±12.55	61.35±10.44	0.068	0.946	NS
LVIDd (1Year)	61.60±12.46	57.45±10.11	1.582	0.117	NS
LVIDd (6-12 diff.)	0.13±1.61	3.10±3.38	-5.515	0.000	S

At shown in above table, after 6 months of therapy, LV internal diastolic diameter decreased by 0.13 mm (SD=1.61) in ACE-I group and 3.10 mm (SD=3.38) in ARNI group with difference reaching statistical significance (p=0.000).

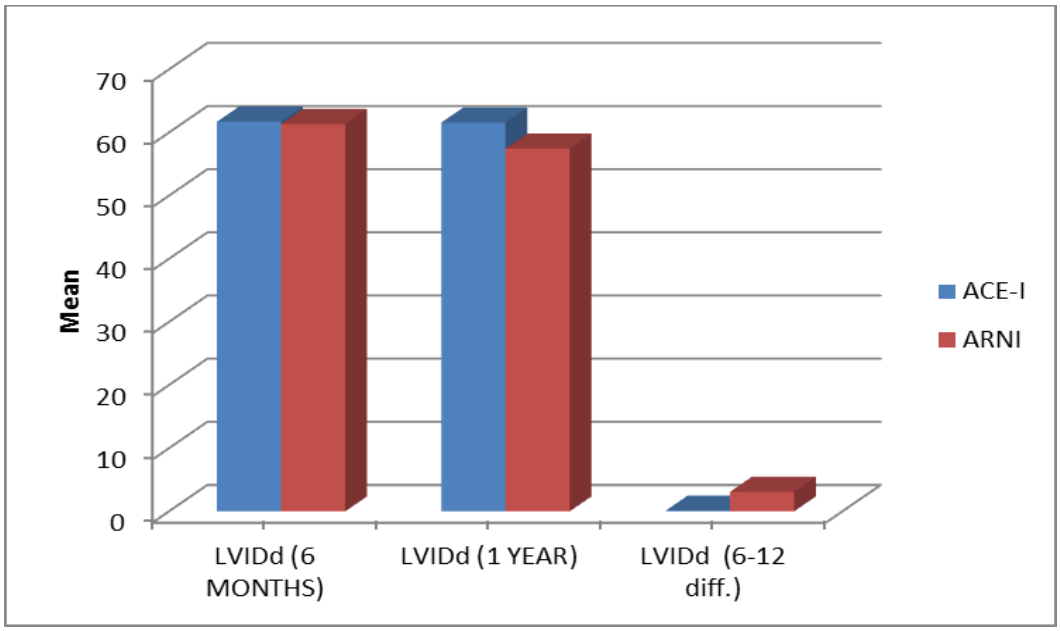


FIGURE 17: Comparison of LV internal diastolic diameter between ACE-I and ARNI group at 6 month follow up

TABLE 18: Comparison of LA diameter between ACE-I and ARNI group at 6 month follow up

	ACE-I	ARNI	T	p-value	Significance
	Mean±SD	Mean±SD			
LA (6Months)	41.33±6.62	41.85±7.65	- 0.342	0.733	NS
LA (1 Year)	41.07±6.64	38.55±6.69	1.688	0.095	NS
LA (6-12 diff)	0.44±2.32	2.81±4.04	- 3.467	0.001	S

As shown in above table, LA size decreased by 0.44 mm (SD=2.32) in ACE-I group and 2.81 mm(SD=4.04) in ARNI group with difference reaching statistical significance(p=0.001).

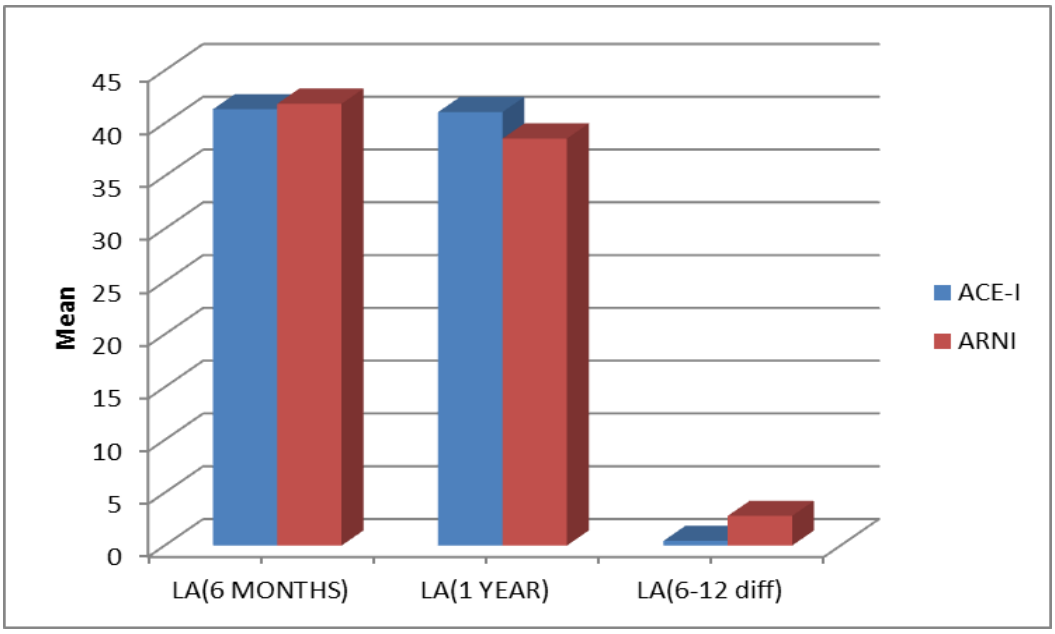


FIGURE 18: Comparison of LA diameter between ACE-I and ARNI group at 6 month follow up.

TABLE 19: Comparison of MVE/A ratio between ACE-I and ARNI group at 6 month follow up.

	ACE-I	ARNI	T	p- value	Significance
	Mean± SD	Mean± SD			
MV E/A (6 Months)	1.17±0.42	1.08±0.46	0.951	0.345	NS
MV E/A (1 Year)	1.20±0.39	1.10±0.26	1.094	0.277	NS
MV E/A (6-12 diff)	-0.02±0.11	-0.11±0.33	1.630	0.107	NS

LV diastolic parameters (MV E/A ratio) were compared in both groups at 6 months and 1 yr of study. No significant difference was observed in both groups after 6 month follow up.

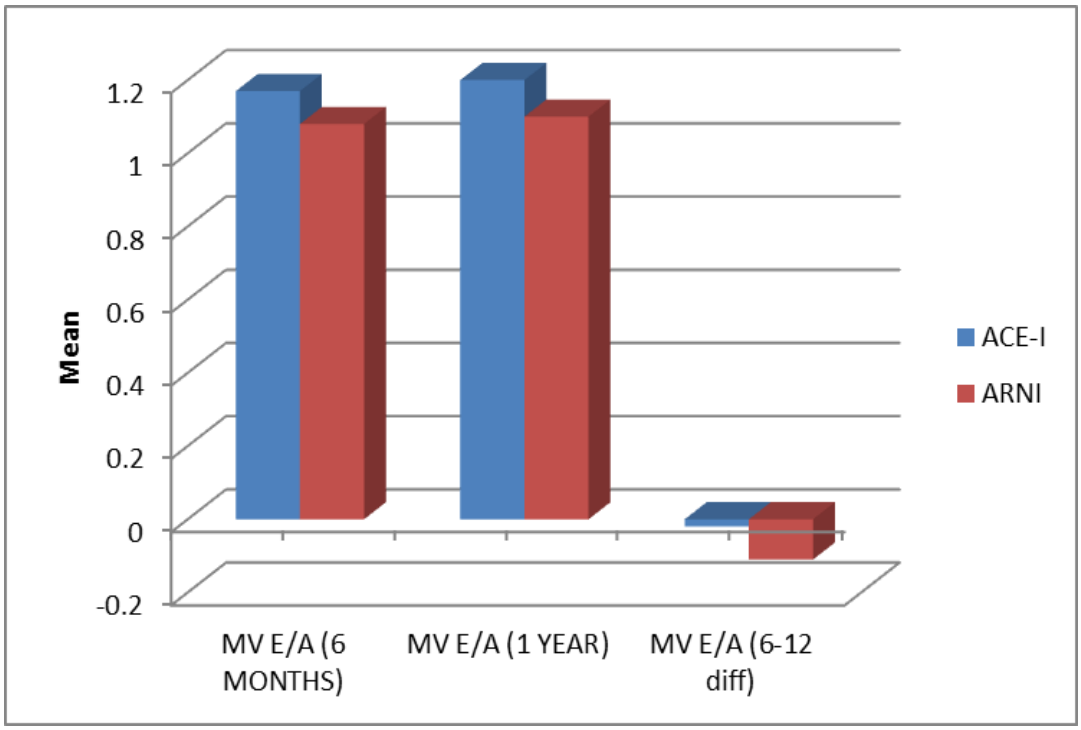


Figure 19: Comparison of MVE/A ratio between ACE-I and ARNI group at 6 month follow up.

TABLE 20: Comparison of PASP between ACE-I and ARNI group at 6 month follow up.

	ACE-I	ARNI	T	p-value	Significance
	Mean± SD	Mean ± SD			
PASP (6Months)	30.23±14.77	32.00±11.17	0.604	0.548	NS
PASP (1 Year)	28.15±12.87	27.48±9.22	0.252	0.802	NS
PASP (6-12 Diff)	2.55±5.60	3.58±7.67	0.718	0.475	NS

As shown in above table, mean PASP decreased by 2.55mm (SD=5.60) in ACE-I group and 3.58mm (SD= 7.67) in ARNI group. No significant difference in decrease in PASP was observed in both groups at 6 month follow up (p=0.475).

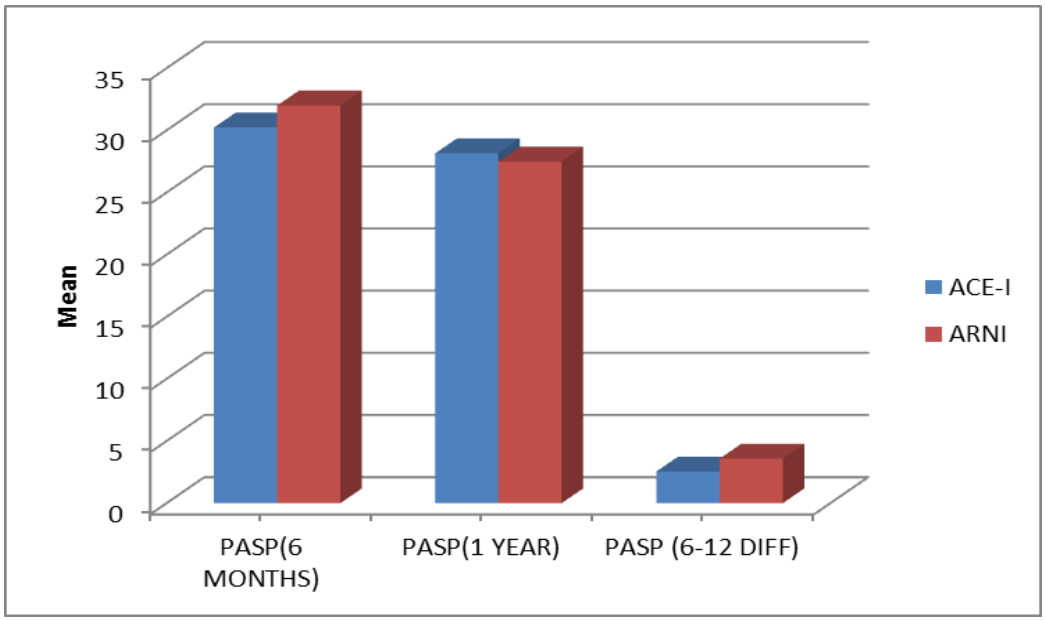


FIGURE 20: Comparison of PASP between ACE-I and ARNI group at 6 month follow up.

TABLE 21: Comparison of TAPSE between ACE-I and ARNI group at 6 month follow up.

	ACE-I	ARNI	T	p-value	Significance
	Mean± SD	Mean± SD			
TAPSE (6Months)	22.63±3.06	22.44±3.23	0.281	0.779	NS
TAPSE (1 Year)	22.78±3.07	22.77±3.20	0.011	0.991	NS
TAPSE (6-12 Diff)	-0.05±0.40	-0.03±1.30	-0.118	0.907	NS

As shown in above table, no significant difference in change in TAPSE was observed after 6 month follow up (p=0.907).

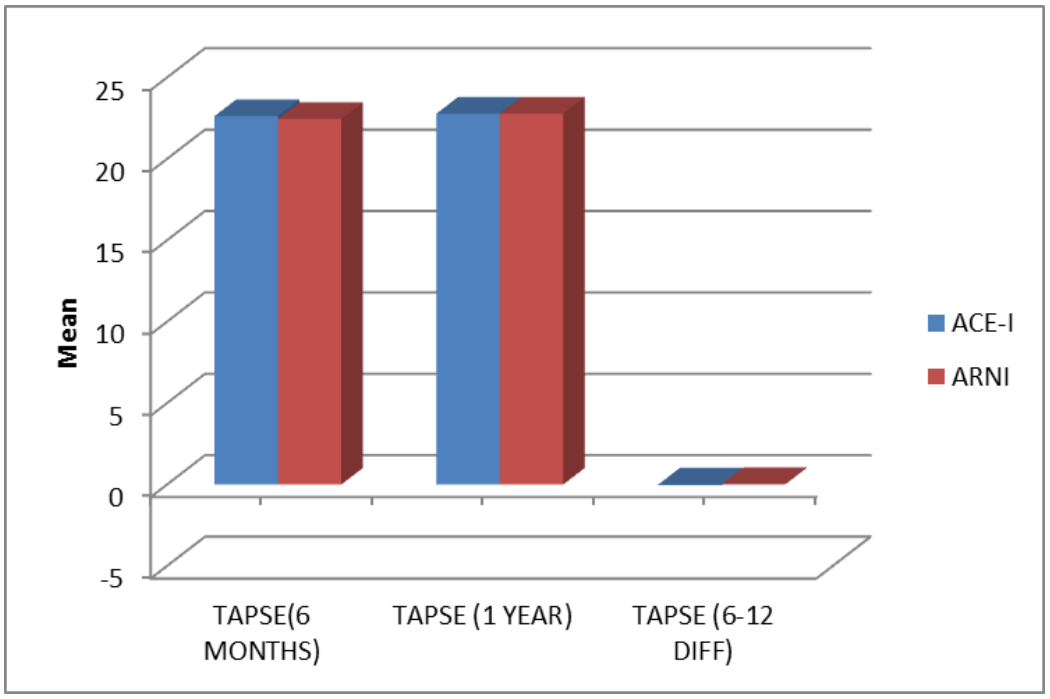


FIGURE 21: Comparison of TAPSE between ACE-I and ARNI group at 6 month follow up.

TABLE 22: Comparison of MR severity between ACE-I and ARNI group

		Group				Chi-square value	p-Value
		ACE-I		ARNI			
MR Severity (6 Months)	MILD MR	16	28.07%	10	29.41%	0.170	0.982
	MOD MR	21	36.84%	12	35.29%		
	SEVERE MR	8	14.04%	4	11.76%		
	NO MR	12	21.05%	8	23.53%		
MR Severity (1 Year)	MILD MR	15	27.27%	22	70.97%	20.758	0.0001
	MOD MR	21	38.18%	1	3.23%		
	SEVERE MR	8	14.55%	1	3.23%		
	NO MR	11	20.00%	7	22.58%		

At time of division into ace-i and arni groups, no difference was found in pt distribution according to MR severity between the groups(p=0.982).After 6 month follow up, 70.97% pts had mild MR in ARNI group as compared to 27.27% in ACE-I group. Pt with Mod MR decreased to 3.23% in ARNI group whereas it was 38.18% in ace-I group. Pts having severe MR were 3.23% in arni and 14.55% in ace-I group. Hence significant reduction in MR severity was seen in ARNI group compared to ACE-I group (p=0.0001).

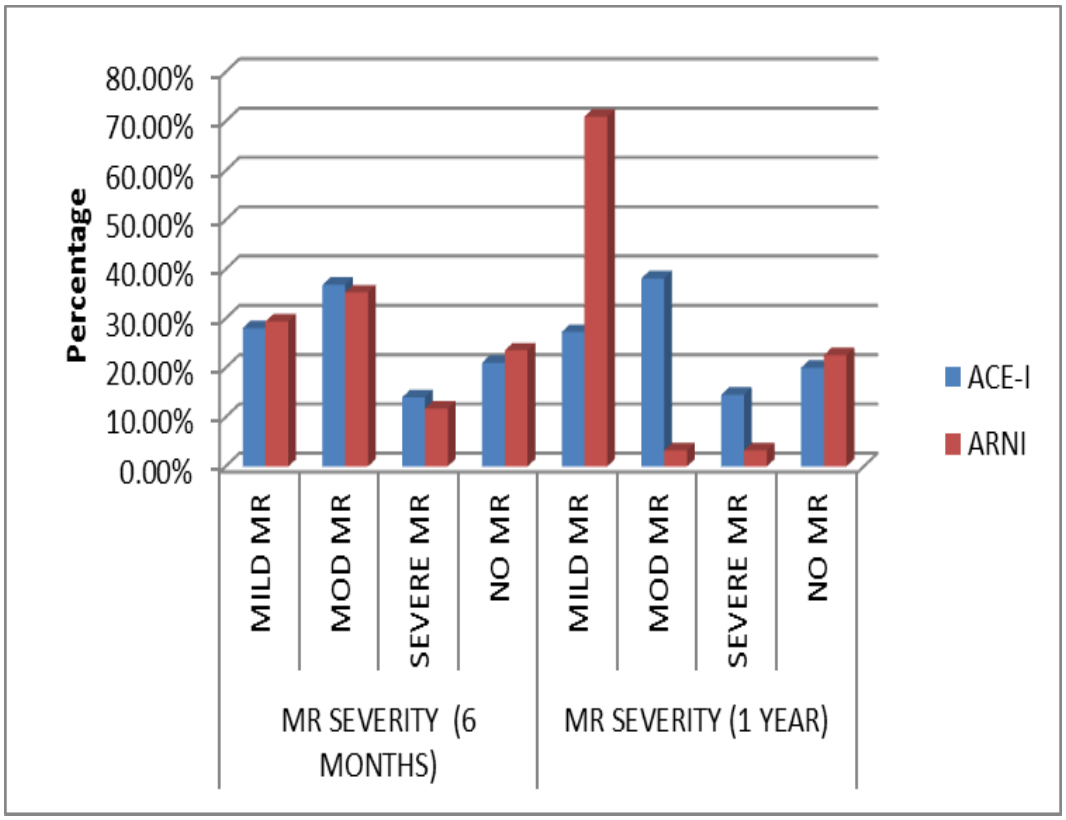


FIGURE 22: Comparison of MR severity between ACE-I and ARNI group

Table 23: Comparison OF NYHA Class between ACE-I and ARNI Group

		Group				Chi-square value	p-value
		ACE-I		ARNI			
NYHA Class (6 Months)	II	27	47.37%	16	47.06%	0.001	0.977
	III	30	52.63%	18	52.94%		
NYHA Class (1 Year)	I	0	0.00%	1	3.23%	8.567	0.014
	II	35	63.64%	27	87.10%		
	III	20	36.36%	3	9.68%		

At time of division into ace-i and arni groups, no difference was found in pt distribution according to NYHA class between the groups (p=0.977). At 6 months follow up , in ace-I group 63.64% pts were in NYHA class II and 36.36% pts were in NYHA class III whereas in arni group, 87.10% pts were in NYHA class II and 9.68% pts were in NYHA class III. Also one pt was in NYHA class I in ARNI group. Significant difference was observed in NYHA classes between ace-I and arni groups at 1 yr of study (p=0.014).

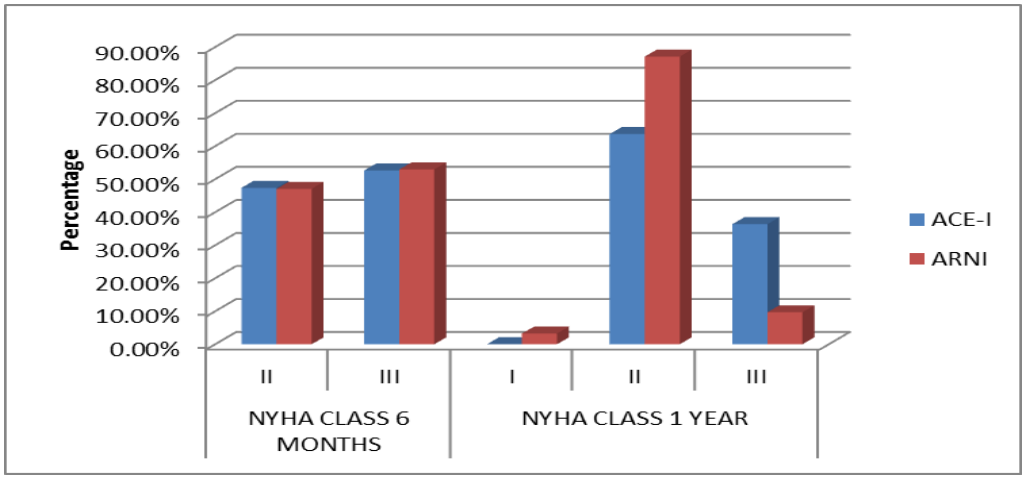
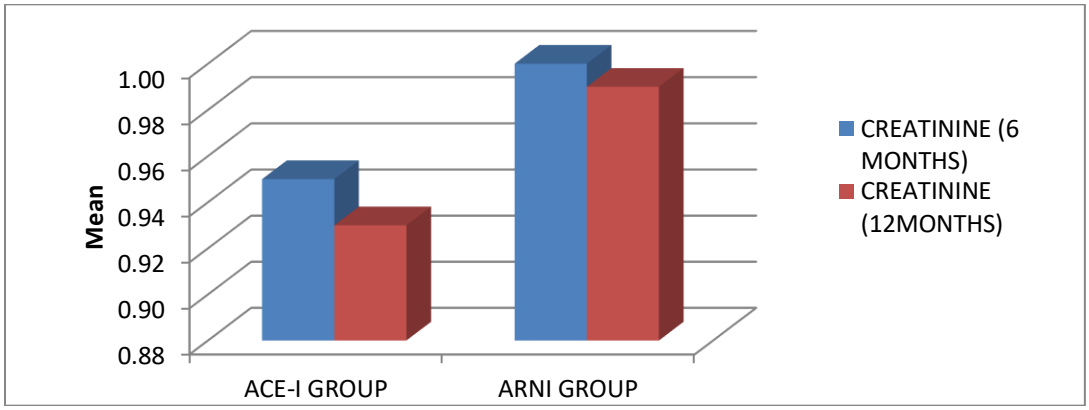


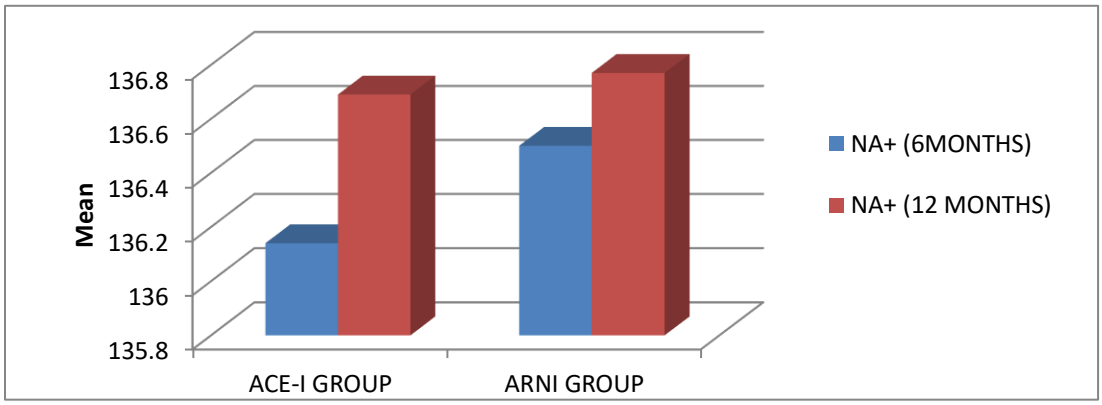
FIGURE 23: Comparison OF NYHA Class between ACE-I and ARNI Group

TABLE 24: Comparison Of Renal Parameters Between ACE-I and ARNI Group at 6 Month Follow up.

	ACE-I GROUP	ARNI GROUP	T	p-value	Significance
	Mean± SD	Mean± SD			
CREATININE (6 Months)	0.95±0.26	1.00±0.32	-0.780	0.437	NS
CREATININE (12Months)	0.93±0.21	0.99±0.22	-1.373	0.173	NS
NA+ (6Months)	136.14±3.78	136.50±4.10	-0.426	0.671	NS
NA+ (12 Months)	136.69±4.22	136.77±3.58	-0.093	0.926	NS
K+ (6 Months)	4.22±0.35	4.26±0.48	-0.401	0.689	NS
K+ (12 Months)	4.22±0.28	4.26± 0.37	-0.513	0.610	NS

In the above table, renal parameters were compared between ACE-I and ARNI group. No significant difference was observed in creatinine and electrolytes in both groups at 6 months and 12 months of study.





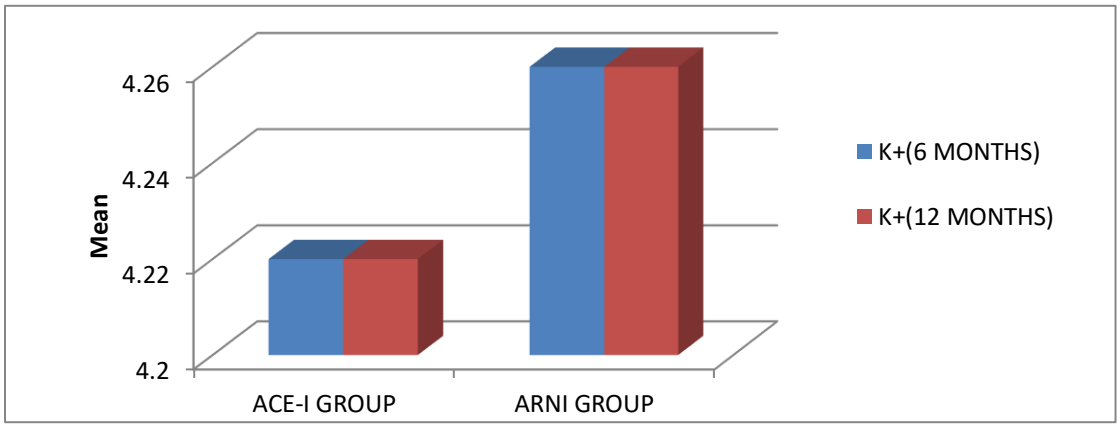


FIGURE 24: Comparison Of Renal Parameters Between ACE-I and ARNI Group at 6 Month Follow up.

TABLE 25: Comparison of adverse events, mortality and hospitalizations in ACE-I and ARNI group

	GROUP						
	ACE-I		ARNI		Total	Chi square Value	p-value
Adverse Events: Hypotension	0	0.00%	1	2.94%	1	1.739	0.187
HOSP 6-12M	5	8.33%	2	5.88%	7	0.189	0.664
MORT 6-12M	0	0.00%	1	2.94%	1	1.739	0.187

One pt in ARNI group had symptomatic hypotension (p=0.187).

3 patients developed cough with ace-I during initial 6 months of study which led to discontinuation of drug.

Total mortality in study was 7 patients. 6 patients died in initial 6 months while on ACE-I therapy.During 6-12 months of study, 1 patient expired in ARNI group.

There were 9 hospitalisations in first 6 months.During 6-12 month period, there were 5 hospitalisations in ACE-I group and 2 hospitalisations in ARNI group.

No significant difference was observed in adverse events, hospitalizations and mortality in both groups.

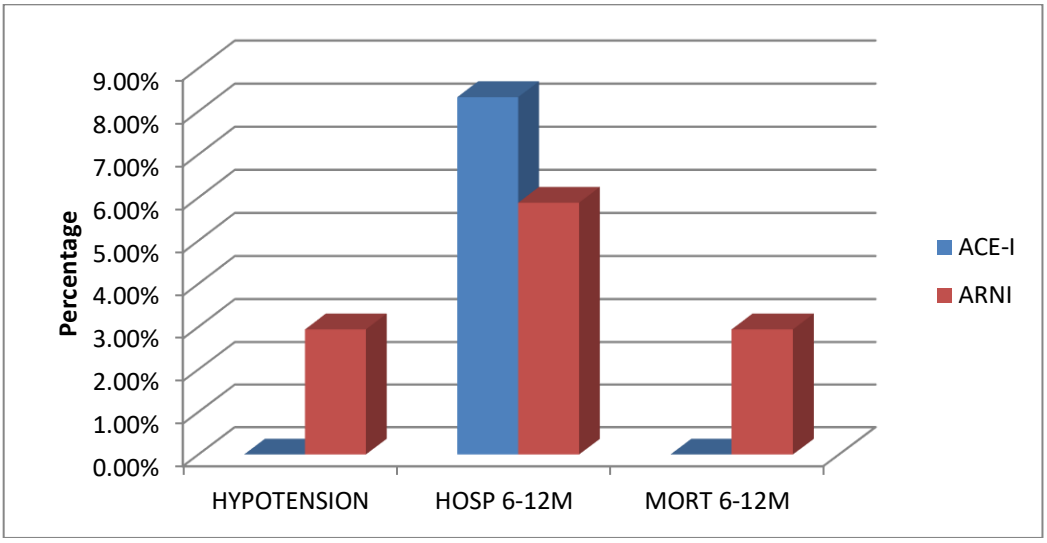


FIGURE 25: Comparison of adverse events, mortality and hospitalizations in ACE-I and ARNI group

TABLE 26: Patients lost to follow up in ACE-I and ARNI group.

		Group				Chi-square value	p-value
		ACE-I		ARNI			
Loss to Follow up	N	55	91.67%	32	94.12%	0.285	0.593
	Y	2	3.51%	2	5.88%		

2 patients in each group were lost to follow up.

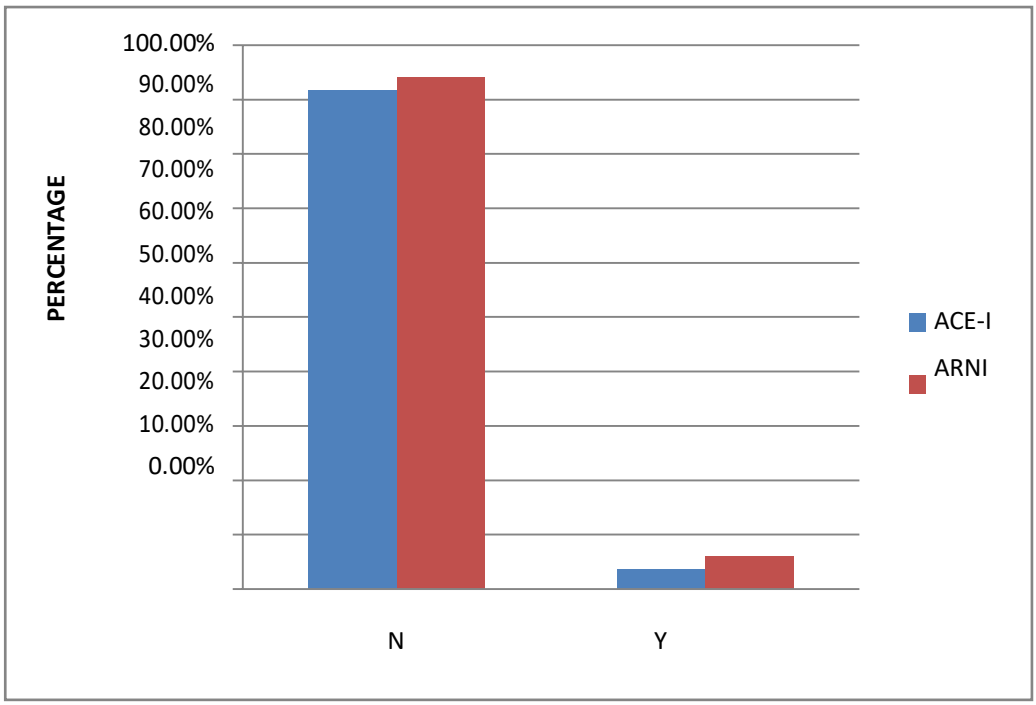


FIGURE 26: Patients lost to follow up in ACE-I and ARNI group.

DISCUSSION

In our study, 100 pts were recruited at baseline. The mean age of study population was 60.07 ± 10.531. 68% patients were male. 80% pts were suffering from ischemic cardiomyopathy. Mean BNP of the study population was 855.95± 905.75. All patients were receiving ACE-Inhibitors and diuretics. 47patients (47%) were on beta blocker therapy, 45 patients (45%) were receiving mineralocorticoid receptor blockers. All patients were followed up for 6 months while on ACE-I therapy. No significant improvement in Echo parameters or functional status including 6 minute walk distance was observed at 6 months of follow up. Therafter, patients were divided into two groups-one group consisting of 34 pts were switched to ARNI while second group constituting 57 pts continued on ACE-I. Pts were thereafter followed up for additional 6 months.

Both ARNI and ACE-I groups were matched and no significant difference was observed in baseline characteristics such as age, sex, comorbidities and baseline therapy in both groups.

Most of the patients in ARNI group were on low dose sacubitril/valsartan (49/51 mg) with one patient receiving upto 200mg and one patient titrated upto 400 mg daily dose.

Comparison was done between both groups regarding Echo parameters and functional status at time of division into two groups and after 6 months of therapy. Also, these parameters were compared at both time intervals in each group. Creatinine and electrolytes were comparable in both groups intitially and no significant differences were observed after 6 month follow up.

TABLE 27: Effect of ARNI therapy on LVEF in various studies.

	EF pre ARNI (%±SD)	EF post ARNI (%±SD)	p-value
Almufleh et al[29]	25.33	30.14	p<0.001
Geoffrey Bayard et al[44]	32.6 ± 5	36 ± 6	p<0.0001
James L. JanuzziJr et al[43]	28.2	34.1	p<0.001
Present study	31.23±4.82	35.68±5.57	p=0.000

Table No.27 shows the effect of ARNI therapy on LVEF in various studies. In our study, Mean lvef improved by 4.45% (SD=4.35) on treatment with ARNI. On the other hand, no significant improvement was noted with ACE-I therapy. This is in accordance with study by Almufleh et al.[29] which demonstrated unchanged LVEF over 6-12 months on stable ACEI/ARB, BB and MRA treatments preceding Sacubitril/Valsartan initiation, followed by a significant improvement in LVEF after its initiation with median duration of treatment being 3 months. This is also in accordance with study conducted by Geoffrey Bayard et al in 2019[44] which demonstrated significant improvement in LVEF after three months of optimal sacubitril valsartan treatment.

A study conducted by James L JanuzziJr et al in 2019.[43] demonstrated significant improvement in LVEF in HfrEF patients on treatment with sacubitril valsartan. Compared with baseline, the 6 month improvements in LVEF was 5.2% (95%CI, 4.8%to 5.6%) (p- value<0.001).

TABLE 28: Effect of ARNI therapy on LVIDs in various studies.

	LVIDs pre ARNI (mm±SD)	LVIDs post ARNI (mm±SD)	p-value
Almufleh et al.[29]	56.3	52.9	0.038
Present study	49.26±8.53	44.77±9.03	0.000

TABLE 29: Effect of ARNI therapy on LVIDd in various studies.

	LVIDd pre ARNI(mm±SD)	LVIDd post ARNI(mm±SD)	p-value
Almufleh et al[29]	65.8	63.15	0.022
Geoffrey Bayard et al[44]	60±4	57±5	0.0002
MatteoLandolfo et al[48]	60 ± 7	56 ± 6	< .001
Present study	60.55±10.13	57.45±10.11	0.000

As shown in tables 28 and 29, in our study, LV internal systolic and diastolic diameters demonstrated significant reduction of 4.48 mm and 3.10 mm respectively over 6 months of treatment with ARNI whereas no significant reduction was observed in ACE-I group (0.35 & 0.13 mm respectively). This is in accordance with study conducted by Almufleh et al.[29] which demonstrated significant reductions in LV end systolic diameter (3.36±1.6 mm) and LV end diastolic diameter (2.64±1.1 mm) after 3 months of therapy with ARNI in patients with HFrEF who had symptomatic heart failure despite optimal ACEI, BB, and MRA treatment.
LV end diastolic diameter also decreased significantly from 60±4 to 57±5mm (p=0.0002) after 3 months of optimal sacubitril valsartan therapy in study conducted by Geoffrey Bayard et al in 2019.[44] A study conducted by MatteoLandolfo et al in year 2020.[48] also demonstrated significant reduction in LVIDd after 3 months of sacubitril valsartan therapy.

TABLE 30: Effect of ARNI therapy on LA diameter in various studies.

	LA diameter pre ARNI (mm±SD)	LA diameter Post ARNI(mm±SD)	p-value
MatteoLandolfo et al [48]	50 ± 8	44 ± 10	<0.05
Present study	41.35± 7.71	38.55± 6.69	0.001

In our study, significant reduction in LA diameter was observed after ARNI therapy whereas no significant reduction resulted with ACE-I therapy. A study conducted by MatteoLandolfo et al [48]in year 2020 also demonstrated significant reduction in LA diameters which reduced from 50 ± 8 mm at baseline to 48 ± 8 mm after 3 months which further reduced to 44±10 after 12 months of sacubitril valsartan therapy in patients with HFrEF as shown in table no. 30.

TABLE 31: Effect of ARNI therapy on PASP in various studies.

	PASP pre ARNI (mm Hg±SD)	PASP post ARNI (mmHg±SD)	p-value
Almufleh et al[29]	29.8	27.51	0.222
Geoffrey Bayard et al[44]	39 ± 10	32 ± 8	<0.0001
MatteoLandolfo et al[48]	38.8 ± 10.7	32.4 ± 12.2	<0.05
Present study	31.06 ±10.87	27.48±9.22	0.014

In our study, PASP decreased significantly in both groups but the reduction was greater in ARNI as compared to ACE-I group. This is consistent with study conducted by Almufleh et al [29] which demonstrated

2.3 mm Hg reduction in PASP with sacubitril valsartan therapy. Geoffrey Bayard et al[44] also demonstrated significant reduction of 7 mm Hg in pulmonary artery systolic pressure with ARNI. MatteoLandolfo et al.[48] also reported significant reduction in pa pressures in HFrEF patients after 1 yr of sacubitril valsartan therapy. Table No.31 shows the effect of ARNI therapy on PASP in various studies.

In our study, no significant changes were observed in LV diastolic parameters or RV functions with ARNI over 6 months. No significant difference in these parameters was observed between ACE-I and ARNI group. Also, there was absence of sinus rhythm in 13 pts due to atrial fibrillation. Of note is that, sufficiently high number of pts with right ventricular dysfunction was lacking. Hence, impact of RV function was difficult to analyze in the study.

In our study, significant reduction in MR severity was noted in ARNI group as compared to ACE-I group. In ARNI group, 47% of pts were in moderate and severe MR category initially which reduced to 6% after 6 months of ARNI therapy whereas no such benefit was observed in ACE-I group. This finding was in accordance with study conducted by ***Kang & Park et al*** **[47]** which concluded that among patients with secondary functional MR, sacubitril/valsartan reduced MR to a greater extent than did valsartan.

TABLE 32: Effect of ARNI therapy on 6MWD in various studies.

	6 MWD pre ARNI (m±SD)	6 MWD post ARNI (m±SD)	p-value
Raquel RodilFraile et al[38]	223.44 ± 93.55	279.12 ± 104.81	<0.001
MerceFaraudo et al[34]	274±96	335±100	0.05
Present study	281.55±57.06	384.34±60.42	0.000

In our study significant improvement was noted in 6 minute walk distance in ARNI group over 6 months in contrast to ACE-I group. This agreed with findings in previous studies conducted by Raquel RodilFraile et al [38] in yr 2018 and MerceFaraudo et al[34] in 2017 as shown in table no. 32.

TABLE 33: Effect of ARNI therapy on NYHA class in various studies.

	NYHA SCALE	NYHA CLASS pre arni *(n,*%)	NYHA CLASS post arni *(n,*%)
Raquel RodilFraile et al.[38]	CLASSII	1 (1)	33 (51)
	Class III	16 (25)	26 (40)
	Class IV	48 (74)	6 (9)
MatteoLandolfo et al.[48]	CLASS I	0 [0%]	26 [53%]
	CLASS II	36 [36%]	23 [47%]
	CLASS III	13 [26.5%]	0 [0%]
Present study	CLASS I	0	1(3.23%)
	CLASS II	16 (47.06)	27(87.10%)
	CLASS III	18 (52.94)	3(9.68%)

As shown in table no.33, improvement in functional status was observed with arni treatment. Over 6 months of therapy, percentage of patients in NYHA class III decreased from 52.94% to 9.68% in arni group and 52.63% to 36.36% in ace-i group. These results were comparable to studies conducted by Raquel Rodil Fraile et al[38] in 2018 and matteolandolfo et al.[48] in year 2020.

In our study, one pt in ARNI group had symptomatic hypotension whereas no pt in ACE-I group suffered from hypotension (p-value=0.187). No patient in either group developed potassium of more than 5.5 meq/l or deterioration in renal function. Hospitalization rate was higher (8.33%) in ACE-I group during as compared to 5.88% in ARNI group, however the difference was non significant (p-value=0.664). These findings correlated well with study conducted by R. De Vecchis et al[36], in which 15.9% of patients on sacubitril/valsartan developed hypotension versus 5.7% in the controls. Also, HF hospitalizations in the study conducted by R. De Vecchis et al were 4.5% in the sacubitril/ valsartan group versus 59% in the conventional therapy group comprising beta-blockers, ACE inhibitors or ARBs plus MRAs.

In our study, mortality was comparable in both ARNI and ACE-I groups with 1 mortality in ARNI group (p value=0.187). One reason for no significant hospitalization and mortality benefit with ARNI therapy observed in our study could be short follow up as previous studies such as Paradigm HF study[21] showed significant hospitalization and mortality benefit with ARNI therapy over median follow up of 27 months.

2pts in ACE-I group and 2 patients in ARNI group were lost to follow up. One reason for lost to follow up was covid 19 outbreak leading to lockdown being imposed resulting in various patients citing transport difficulties and resorting to treatment from local centres.

Our study provided a direct comparison of ARNI to ace-i therapy. All patients were initially on ACE-I in addition to OMT prior to initiating Sacubitril/Valsartan during which no significant improvements were noted in echo parameters or functional status of the patients. Furtheremore, patients who were continued on ACE-I therapy didn’t show any significant improvement at 1 yr of study whereas patients who opted for Sacubitril/Valsartan had significant improvement in functional status and

echo parameters. Hence, this suggests that improvements seen in ARNI group are very likely attributable to Sacubitril/Valsartan.

LIMITATIONS

1. This was a single centre study.
2. Small sample size with only 34 patients opting for ARNI therapy, one reason being costly medication.
3. Short follow up.
4. It was a non blinded study.

SUMMARY AND CONCLUSION

The present study was conducted to access effects of ARNI therapy on clinical parameters and echocardiographic features in HFrEF patients as compared to ACE Inhibitors.

1. ARNI therapy resulted in significant improvement in clinical parameters i.e. 6 minute walk distance and NYHA class compared to ACE-I therapy.
2. Greater rise in ejection fraction was noted with ARNI therapy in comparison to ACE-I therapy.
3. LV systolic and diastolic dimensions and LA diameter decreased significantly with ARNI therapy compared to ACE-I.
4. Severity of MR decreased significantly in patients with ARNI therapy compared to ACE-I
5. No change in LV diastolic parameters and RV function was noted in either group.
6. Patients in both groups were matched in various parameters such as age, sex, etiology of heart failure, comorbidities, baseline medical therapy such as beta blockers, mineralocorticoid receptor antagonists.
7. Most of the patients in ARNI group remained on low dose sacubitril/valsartan.
8. No significant difference in adverse events was noted between both groups.
9. Mortality and hospitalizations did not differ significantly in ACE-I and ARNI groups.

In conclusion, ARNI therapy resulted in greater and significant reverse remodeling and improvement in functional status in comparison to ACE-I therapy in patients with Heart failure and reduced EF. However, to establish the hypothesis on firm footing, further studies are needed.

BIBLIOGRAPHY

1. Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB et al. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. JACC Heart Fail. 2014;2:97-112.
2. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007;93:1137-46.
3. Bleumink GS, Knetsch AM, Sturkenboom MCJM, Straus SMJM, Hofman A, Deckers JW, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam study. Eur Heart J England. 2004;25:1614-9.
4. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, et al. EUR Observational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail. 2013;15:808-17.
5. Pocock SJ, Ariti CA, McMurray JJV, Maggioni A, Køber L, Squire IB, et al,. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013;34:1404-13.
6. Harikrishnan S, Sanjay G, Anees T, Vishwanathan S, Vijayaraghavan G, Bahuleyan CG, et al. Clinical presentation, management, In-hospital and 90-day outcomes of heart failure patients in Trivandrum, Kerala, India : the Trivandrum Heart Failure Registry. European journal of heart failure. 2015;17:794-800.
7. HishamDokainish, Koon Teo, Jun Zhu, Ambuj Roy, Khalid F AlHabib, Ahmed ElSayed et al. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. Lancet Glob Health. 2017, 5:e665-e672.
8. Seth S, Ramakrishnan S, Parekh N, Karthikeyan G, Singh S, Sharma G. Heart failure guidelines for India: Update 2017. J Pract Cardiovasc Sci 2017;3:133-8.

9. McMurray JJ V. Clinical practice. Systolic heart failure. N Engl J Med. 2010;3623:228-38.
10. Krishnaswamy P, Lubien E, Clopton P, Koon J, Kazanegra R, Wanner E. Utility of B-natriuretic peptide levels in identifying patients with left ventricular systolic or diastolic dysfunction. Am J Med. 2001;111:274-9.
11. Roberts E, Ludman AJ, Dworzynski K, Al-Mohammad A, Cowie MR, McMurray JJV, et al. The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting. BMJ 2015;350:h910.
12. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16:233-70.
13. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J. 1998;135:825–32.
14. Nakagawa O, Ogawa Y, Itoh H, Suga S, Komatsu Y, Kishimoto I, et al Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy. Evidence for brain natriuretic peptide as an “emergency” cardiac hormone against ventricular overload. JClin Invest 19958;96:1280–7.
15. De Vecchis R, Esposito C, Cantatrione S Natriuretic peptide-guided therapy: further research required for still-unresolved issues. Herz 2013;38:618–28.
16. MaiselA,Mueller C, Adams K Jr et al State of the art: using natriuretic peptide levels in clinical practice. EurJ Heart Fail 2008;10:824–39.
17. Gu J, Noe A, Chandra P, Al-Fayoumi S, Ligueros- SaylanM, SarangapaniR, Pharmacokinetics and pharmacodynamics of LCZ696, a

novel dual-acting angiotensin receptor neprilysin inhibitor (ARNi). J Clin Pharmacol 2010;50:401–14.

18. Massimo Volpe, Speranza Rubattu, and Allegra Battistoni; ARNi: A Novel Approach to Counteract Cardiovascular Diseases. Int J Mol Sci. 2019; 20:2092.
19. P. Ponikowski, Adriaan A. Voors, Stefan D. Anker, He´ctorBueno, John G. F. Cleland, Andrew J. S. Coats et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2016; 37: 2129–200.
20. Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation 2002;106:920–6.
21. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz M, Rizkala AR, PARADIGM-HF Investigators and Committees. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004.
22. Vodovar N, Paquet C, Mebazaa A, Launay J-M, Hugon J, Cohen-Solal A. Neprilysin, cardiovascular, and Alzheimer"s diseases: the therapeutic split? Eur Heart J. 2015;36:902-5.
23. Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. The neurohumoral axis in congestive heart failure. Ann Intern Med 1984;101:370-7.
24. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuro endocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A sub study of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation 1990;82:1724-9.
25. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on

Cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000;35:569-82.

26. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation. 1987;76:44–51.
27. Mentz RJ, Bakris GL, Waeber B, McMurray JJ, Gheorghiade M, Ruilope LM, et al. The past, present and future of renin–angiotensin aldosterone system inhibition. Int J Cardiol. 2013;167:1677–87.
28. Von Lueder T, Wang B, Kompa A, Huang L, Webb R, Jordan P,et al. Angiotensin receptor neprilysin inhibition (ARNI) attenuates adverse cardiac remodeling in vitro and in vivo. Heart Lung Circ. 2013;22:71.
29. Almufleh A, Marbach J, Chih S, Stadnick E, Davies R, Liu P, et al. Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in heart failure with reduced ejection fraction patients. Am J Cardio vasc Dis. 2017;7:108-13.
30. Ishii M, Kaikita K, Sato K, Sueta D, Fujisue K, Arima Y, et al. Cardioprotective Effects of SACUBITRIL/VALSARTAN (Sacubitril/Valsartan) After Experimental Acute Myocardial Infarction. JACC. 2017;2:655-68.
31. Nazzari H, Yeung M, Marceau A, Luong M, Clark C, Ahuja S, et al. Left Ventricular Function Improves in Heart Failure Patients Treated with Sacubitril-Valsartan. Can J Cardiol. 2017;33:163.
32. Maurin V, Canu A, Bernard A, Lafitte S, Picard F. Early reverse remodeling and improvement of echo parameters after introduction of sacubitril/valsartan in 80 stable and well treated HFrEF patients. Eur J Heart Fail. 2017;19:296.
33. Groba-Marco M, Singh M, Galvan Ruiz M, Fernandez-De-Sanmamed-Giron M, Montiel Quintero R, Perez-Nogales E, et al. Early left ventricular reverse remodeling after sacubitril/valsartan treatment in clinical practice. Eur J Heart Fail. 2017; 20:225.
34. MerceFaraudo, Paola Beltran, Roman Freixa, Elisabet Mena, Olga Guri, Anna Contra, et al.Does Angiotensin Receptor Neprilysin Inhibitor

(ARNI) Improve Functional Capacity Assessed by 6 Minutes Walking Test? EurCardiol. 2017;12:100.

35. HlavataK, Hoskova L, Franekova J, Jabor A, Kautzner J, Melenovsky V, etal, Transition from angiotensin-converting enzyme inhibitor/angiotensin-II-receptor-blocker to sacubitril/valsartan in chronic heart failure patients: Initial experiences in clinical practice, Cor et Vasa 2018;60:209-14.
36. De Vecchis R, Ariano C, Di Biase G, Noutsias M. Sacubitril/valsartan for heart failure with reduced left ventricular ejection fraction: A retrospective cohort study. Herz. 2019;44:425-32.
37. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, *et al.* Angiotensin–Neprilysin Inhibition in acute decompensated heart failure. N Engl J Med. 2019;380:539-48
38. RodilFraile R, Malafarina V, Tiberio Lopez G. Sacubitril-valsartan in heart failure and multi morbidity patients. ESC Heart Failure. 2018; 5:957-60.
39. Kalantari S, Medvedofsky DM, Grinstein JG, Tayazime ST, Kim GK, Sarswat NS, et al Remodel: Demonstration of Reverse Remodeling Effects of sacubitril/valsartan. Eur J Heart Fail. 2017; 20:36- 7.
40. De Diego C, González-Torres L, Núñez JM, Centurión ER, De Lara G, Macias M. Angiotensin neprilysin inhibition further reverses cardiac remodeling as compared to angiotensin inhibition in reduced heart failure patients. Europace. 2018;20:139.
41. Martens P, Beliën H, Dupont M, Vandervoort P, Mullens W. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. Cardiovascular Therapeutics. 2018; 36: 12435.

42. Daubert MA, Adams K, Yow E, et al. NT-proBNP goal achievement is associated with significant reverse remodeling and improved clinical outcomes in HFrEF. JACC Heart Fail. 2019;7:158-68.
43. Januzzi JL, Prescott MF, Butler J, et al. Association of Change in N-Terminal Pro–B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment with Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction. *JAMA.* 2019;322:1085–95.
44. Geoffrey Bayard, Antoine Da Costa, Romain Pierrard, Cécile Roméyer-Bouchard, Jean Baptiste Guichard, and Karl Isaaz. Impact of sacubitril/valsartan on echo parameters in heart failure patients with reduced ejection fraction a prospective evaluation. Int J Cardiol Heart Vasc. 2019; 25:100418.
45. Yiwen Wang, Ran Zhou,Chi Lu,Qing Chen, TongdaXu, and Dongye Li. Effects of the Angiotensin Receptor Neprilysin Inhibitor on Cardiac Reverse Remodeling: Meta Analysis.J Am Heart Assoc. 2019;8: 012272
46. Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol.2015;65:1231-48.
47. Kang DH, Park SJ, Shin SH, Hong GR, Lee S, Kim MS, Yuet al. Angiotensin Receptor Neprilysin Inhibitor for Functional Mitral Regurgitation. Circulation. 2019;139:1354-65.
48. MatteoLandolfo, Federica Piani, Daniela Degli Esposti, Eugenio Cosentino, Stefano Bacchelli, Ada Dormi, Claudio Borghi. Effects of sacubitril valsartan on clinical and echocardiographic parameters of outpatients with heart failure and reduced ejection fraction. IJC Heart & Vasculature 2020;31:100656.
49. Li-Wei Liu, Po-Ching Wu, Mei-Ya Chiu, Pei-Fen Tu and Ching-Chang Fang. Sacubitril/Valsartan Improves Left Ventricular Ejection Fraction and Reverses Cardiac Remodeling in Taiwanese Patients with Heart

Failure and Reduced Ejection Fraction, Acta Cardiol Sin 2020;36:125-32.

50. Boston ML. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. The Criteria Committee of the New York Heart Association 1994:253-6.
51. Wasserman K, Hansen JE, Sue DY, Whipp BJ, Froelicher VF. Principles of exercise testing and interpretation. Journal of Cardiopulmonary Rehabilitation and Prevention. 1987;189.
52. Lang RM, Bierig M, Devereux RB. Recommendations for chamber quantification.J Am Soc Echocardiogr.2005;18:1440-6.

							PAST HISTORY								Baseline Medications												Creatinine							SODIUM					
Sr. No	Group	Name	AGE/SEX	ETIOLOGY OF HEART FAILURE	MRD.NO	COMPLAINTS	DM	HTN	CKD	CAD	COPD	CVA	THYROID	AF	Beta Blockers	ACE-I	ARBS	CCB	MRA	DIURETICS	IVABRADINE	DIGOXIN	PPI/CRT	ICD	BNP	ECG	BASELINE	2 MONTHS	4 MONTHS	6 MONTHS	8 MONTHS	10 MONTHS	12 MONTHS	BASELINE	2 MONTHS	4 MONTHS	6 MONTHS	8 MONTHS	10 MONTHS
1	ACE-I	DP	49/M	ICMP	720602	DOE	Y	N	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	98	RBBB NSR	0.5	0.6	0.7	0.7	0.5	0.6	0.6	136	136	140	135	136	130
2	ACE-I	BS	64/M	ICMP	202314	DOE	N	N	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	480	NSR	0.8	0.8	0.7	0.8	0.8	0.9	0.8	140	140	136	131	130	132
3	ACE-I	SK	52/M	ICMP	512618	DOE	Y	Y	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	1370	RBBB NSR	1.02	0.9	0.9	1	0.9	0.9	1	138	135	130	136	139	140
4	ACE-I	NK	50/M	ICMP	719987	DOE	N	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	92	NSR	0.83	0.8	0.8	0.9	0.8	0.8	1	137	136	134	135	130	132
5	ARNI	NS	53/F	ICMP	424860	DOE	Y	Y	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	147	NSR	0.5	0.7	0.8	1	0.9	1	0.96	137	135	136	132	139	138
6	ACE-I	GS	55/M	ICMP	720599	CHEST PAIN	N	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	112	NSR	0.9	0.8	0.8	0.9	0.9	1	0.1	136	142	138	137	136	138
7	ARNI	AK	70/F	ICMP	720073	DOE	N	N	N	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	680	NSR	1.4	1	1.6	1.7	-	-	-	130	132	130	140	-	-
8	ACE-I	DS	63/M	ICMP	190642	DOE	N	N	N	Y	N	N	N	Y	N	Y	N	N	Y	Y	N	N	N	N	1372	AF RBBB	1.06	1	1.1	1	1.1	1	1.1	134	138	136	136	138	139
9	ACE-I	DS	55/M	DCMP	721412	DOE	N	N	N	N	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	812	NSR	0.7	0.83	1.3	1.3	1.2	1.2	1.1	141	134	135	136	132	134
10	ARNI	PK	72/M	ICMP	179025	DOE	Y	N	N	y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	1930	NSR	1.22	1.23	1.22	1.27	-	-	-	128	134	140	144	-	-
11	ARNI	HS	65/M	DCMP	711631	DOE	Y	N	N	N	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	223	NSR	0.8	0.7	0.8	1	0.9	0.8	0.9	137	144	140	138	141	142
12	ARNI	RB	60/M	ICMP	644531	CHEST PAIN/DOE	N	Y	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	796	LAFB NSR	0.6	1	0.7	0.7	0.8	0.8	0.9	140	127	124	135	130	128
13	ARNI	PK	60/F	DCMP	483957	DOE	N	N	N	N	N	N	N	N	N	Y	N	N	Y	Y	Y	N	N	N	5	NSR	0.7	0.6	0.8	0.7	0.8	0.9	0.8	137	140	135	128	137	138
14	ACE-I	SR	45/F	ICMP	552428	DOE	N	N	N	Y	N	N	Y	N	N	Y	N	N	Y	Y	N	N	N	N	48	LAFB NSR	0.6	0.7	0.8	0.9	0.8	0.8	0.8	138	138	136	140	138	129
15	ACE-I	LJ	71/F	ICMP	342820	DOE	N	N	N	Y	N	N	N	N	N	Y	N	Y	Y	Y	N	N	N	N	225	NSR	0.8	0.8	0.78	0.8	0.9	0.8	0.8	138	136	130	135	139	142
16	ACE-I	GK	65/F	DCMP	701589	DOE	Y	N	N	N	N	N	Y	Y	Y	N	N	N	Y	N	N	N	N	N	112	AF	1.3	1.4	1.5	1.7	1.4	1.4	1.2	136	140	142	139	128	129
17	ACE-I	KG	62/F	ICMP	722936	DOE	Y	Y	N	Y	N	N	N	N	N	Y	N	Y	N	Y	N	N	N	N	1570	NSR	1	1.39	1.2	1.9	1.5	1.3	1.3	133	136	134	130	135	136
18	ACE-I	RR	56/F	ICMP	77496	DOE	Y	Y	N	Y	N	N	N	N	N	Y	N	N	Y	Y	Y	N	N	N	1120	LAFB NSR	0.4	0.6	0.5	0.4	0.6	0.5	0.6	136	136	139	139	130	134
19	ACE-I	SK	63/F	ICMP	726231	DOE	Y	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	666	NSR	0.7	-	-	-	-	-	-	130	-	-	-	-	-
20	ACE-I	DS	62/M	ICMP	724467	DOE	Y	N	N	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	748	NSR	0.9	0.8	1	0.9	1	1	0.9	140	140	142	145	137	137
21	ACE-I	PL	72/M	ICMP	267506	DOE	Y	Y	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	263	NSR	1.1	1.2	1.1	1.29	1.2	1.1	1.2	140	130	134	128	130	134
22	ACE-I	SC	61/F	DCMP	725496	DOE	Y	Y	N	N	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	1210	NSR	1.09	1	0.9	0.8	0.9	0.9	0.9	137	138	134	140	139	138
23	ACE-I	DS	79/M	ICMP	156873	DOE	Y	N	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	1110	LBBB NSR	0.8	0.9	0.8	0.9	0.9	0.7	0.9	138	146	138	137	138	139
24	ARNI	GC	67/M	ICMP	727155	DOE	N	Y	N	Y	N	N	N	N	N	Y	N	Y	N	Y	N	N	N	N	1570	NSR	0.9	1.1	1.3	1	1.1	1	1.2	141	136	135	139	140	142
25	ACE-I	AS	61/M	ICMP	728597	DOE	N	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	112	NSR	0.9	0.9	0.8	0.9	0.9	0.9	0.8	138	136	138	136	138	139
26	ARNI	JK	50/F	DCMP	483064	DOE	N	N	N	N	-	N	N	N	N	Y	N	N	N	Y	N	N	N	N	88	LBBB NSR	1.1	1	0.9	0.8	0.9	0.9	0.8	136	139	136	138	140	142
27	ARNI	VN	65/M	NCLV	727882	DOE	Y	Y	N	N	N	N	N	N	Y	Y	N	Y	N	Y	N	N	N	N	5000	LBBB NSR	0.9	0.98	0.8	1	1.1	0.9	0.9	139	134	136	140	143	127
28	ARNI	R	52/M	ICMP	722230	DOE	Y	Y	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	1730	RBBB NSR	1	1.5	0.78	0.82	0.9	0.8	1	137	136	136	140	142	135
29	ACE-I	GK	50/M	ICMP	725304	DOE	Y	N	N	Y	N	N	N	N	Y	N	N	Y	Y	Y	N	N	N	N	1442	AF	0.6	0.7	0.8	0.9	0.8	0.7	0.8	141	136	134	140	143	135
30	ACE-I	RK	65/F	ICMP	728691	CHESTPAIN	Y	Y	N	Y	N	N	N	Y	N	Y	N	N	Y	Y	N	N	N	N	480	AF RBBB	0.6	-	-	-	-	-	-	132	-	-	-	-	-
31	ACE-I	RKS	60/M	ICMP	727929	CHESTPAIN	Y	N	N	Y	N	N	N	N	Y	Y	N	N	Y	Y	Y	N	N	N	36	RBBB NSR	1	1.3	1.2	1.21	1.2	1.1	1.2	138	138	140	137	136	140
32	ACE-I	SK	36/F	ICMP	730170	CHESTPAIN	Y	N	N	Y	N	N	N	Y	Y	Y	N	N	Y	Y	N	N	N	N	1450	AF	0.9	0.8	0.9	0.9	0.8	0.8	0.9	137	143	138	135	129	145
33	ACE-I	ND	64/F	DCMP	51399	DOE	N	N	N	N	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	1140	NSR	1.03	-	-	-	-	-	-	130	-	-	-	-	-
34	ACE-I	GS	69/M	ICMP	195249	CHESTPAIN	N	N	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	71	NSR	1.1	1	1.1	1.1	1	1	1.1	137	136	140	138	128	129
35	ACE-I	SK	53/F	ICMP	262871	CHESTPAIN	Y	Y	N	Y	N	N	N	N	N	Y	N	Y	Y	Y	N	N	N	N	140	NSR	1.5	1.4	1.4	1.5	1.5	1.5	1.4	133	138	139	136	128	135
36	ACE-I	ML	64/M	ICMP	59669	CHESTPAIN	Y	Y	N	Y	N	N	N	Y	N	Y	N	N	N	Y	N	N	N	N	300	AF	1.1	1	1.2	1	1.1	1.1	1.2	138	136	134	138	126	128
37	ACE-I	MK	57/F	DCMP	727107	DOE	Y	Y	N	N	N	N	N	Y	N	Y	N	N	N	Y	N	N	N	N	400	AF	0.6	-	-	-	-	-	-	129	-	-	-	-	-
38	ACE-I	SS	73/M	ICMP	516991	CHESTPAIN	Y	N	N	Y	N	N	N	N	N	Y	N	Y	Y	Y	N	N	N	N	2800	LBBB NSR	1.3	1.2	1.3	1.3	1.1	1.3	1.2	135	136	134	130	136	140
39	ACE-I	HS	43/M	ICMP	729415	DOE	Y	N	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	98	NSR	0.7	0.9	0.9	0.8	0.9	0.7	0.9	137	136	130	135	139	142
40	ACE-I	ML	75/M	ICMP	729981	DOE	Y	Y	N	y	N	N	N	N	N	Y	N	Y	Y	Y	N	N	N	N	2290	NSR	1.3	1.1	1.1	1	0.9	0.9	1	131	140	142	139	128	129
41	ACE-I	NK	44/F	ICMP	730806	DOE	N	N	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	2940	NSR	0.5	0.8	0.9	0.7	0.8	0.8	0.7	143	136	134	130	135	136
42	ACE-I	RM	44/M	DCMP	730842	DOE	Y	Y	N	N	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	1600	NSR	0.6	-	-	-	-	-	-	130	-	-	-	-	-
43	ACE-I	PK	60/M	ICMP	731558	DOE	Y	Y	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	94	NSR	1	1	1	1	1	1.1	1	139	136	139	139	130	134
44	ACE-I	GS	43/M	DCMP	152604	DOE	N	N	N	N	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	84	NSR	1	1	0.9	0.9	1	1	1	146	136	140	131	138	137
45	ACE-I	KK	68/F	ICMP	729836	DOE	N	N	N	Y	N	N	N	N	Y	Y	N	Y	Y	Y	N	N	N	N	82	IVCD NSR	0.7	0.59	0.8	1	1	1	1	133	140	141	133	134	136
46	ACE-I	VK	50/M	ICMP	716248	DOE	Y	Y	N	Y	N	Y	N	Y	Y	Y	N	Y	N	Y	N	N	N	N	442	NSR	1.1	1	1.1	1	0.9	1.2	1	132	140	142	145	137	137
47	ACE-I	MS	60/M	DCMP	729462	DOE	Y	N	N	N	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	2100	AF	0.97	0.9	1	1.1	1.2	1	1.1	137	130	134	128	130	134
48	ARNI	BS	50/M	ICMP	733997	DOE	Y	Y	N	Y	N	N	N	N	N	Y	N	Y	N	Y	N	N	N	N	87	NSR	1.06	0.9	0.8	0.9	0.8	0.9	0.88	141	137	143	138	137	138
49	ACE-I	MS	40/M	ICMP	809889	CHESTPAIN	N	N	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	720	NSR	0.9	0.9	0.8	0.9	-	-	-	134	133	137	135	-	-
50	ARNI	IS	70/M	ICMP	149412	DOE	N	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	812	NSR	0.9	0.8	0.9	1	0.9	0.9	0.8	133	144	132	133	132	134
51	ACE-I	AJ	40/M	ICMP	735231	DOE	N	Y	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	2560	NSR	0.95	0.8	1	1	1	1	0.9	141	139	142	136	134	135
52	ACE-I	SK	69/M	ICMP	164959	DOE	N	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	2531	NSR	1.1	1	1	0.9	0.9	0.8	1	137	137	131	135	136	138
53	ARNI	RJ	72/M	ICMP	671613	DOE	Y	Y	N	Y	N	N	N	Y	N	Y	N	N	N	Y	N	N	N	N	848	AF	0.98	1.05	1	0.96	1.1	1	1	141	135	137	140	139	142
54	ARNI	RK	63/M	ICMP	145313	DOE	Y	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	1010	NSR	1	0.9	0.8	0.8	0.9	0.8	0.8	141	142	138	140	142	143
55	ACE-I	BS	60/M	ICMP	142357	DOE	Y	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	540	NSR	0.9	0.8	0.9	0.7	0.6	0.7	0.8	138	140	138	137	138	140
56	ACE-I	RK	75/M	ICMP	733931	CHESTPAIN	Y	N	N	Y	N	N	N	N	Y	Y	N	Y	Y	Y	N	N	N	N	531	NSR	0.97	0.9	0.8	0.9	0.9	0.8	0.8	133	135	140	140	139	138
57	ACE-I	JS	62/M	DCMP	736149	DOE	N	Y	N	N	N	N	N	N	N	Y	N	N	N	Y	Y	N	N	N	79	NSR	0.8	1.4	1.3	1.3	1	1.1	1.2	138	138	134	140	139	138
58	ACE-I	VK	65/F	ICMP	542524	DOE	N	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	1670	NSR	0.57	0.6	0.7	0.5	0.7	0.8	0.8	137	146	138	137	138	139
59	ACE-I	RPS	50/M	DCMP	735432	PALPITATIONS	Y	N	N	N	N	N	N	Y	N	Y	N	N	N	Y	N	N	N	N	1310	AF	0.6	0.8	0.7	1	0.8	0.8	0.9	133	136	135	139	140	142
60	ACE-I	DD	66/F	ICMP	736155	DOE	Y	Y	N	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	87	NSR	0.6	0.8	0.9	0.8	0.7	0.8	0.8	134	136	138	136	138	139
61	ARNI	HN	38/M	ICMP	736724	DOE	Y	N	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	76	NSR	0.7	0.6	0.7	0.6	0.9	0.8	0.8	141	139	136	138	140	142
62	ACE-I	MC	41/M	DCMP	739196	DOE	N	N	N	N	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	42	NSR	0.7	0.8	0.9	0.8	0.7	0.7	0.8	137	137	141	134	135	139
63	ACE-I	SG	60/F	ICMP	736126	CHESTPAIN	Y	Y	N	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	354	IVCD NSR	0.5	0.8	0.7	0.9	0.6	0.5	0.5	139	136	141	140	138	137
64	ACE-I	RD	44/M	ICMP	147205	DOE	N	N	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	23	NSR	1.5	1.2	0.7	0.81	0.9	0.9	0.9	130	139	142	135	132	139
65	ACE-I	VS	60/M	ICMP	739071	DOE	N	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	980	NSR	0.98	0.8	0.9	0.9	0.7	1	1	141	135	138	137	130	128
66	ACE-I	SS	72/M	ICMP	737828	DOE	Y	Y	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	827	NSR	1.2	1	1.3	1.4	1.2	1	1.1	137	141	144	137	138	130
67	ACE-I	PP	57/M	DCMP	752020	DOE	N	N	N	N	N	N	N	Y	N	Y	N	N	Y	Y	N	N	N	N	1250	AF	1.48	-	-	-	-	-	-	137	-	-	-	-	-
68	ARNI	BS	38/M	DCMP	739270	PALPITATIONS	Y	N	N	N	N	N	N	Y	Y	Y	N	N	Y	Y	N	N	N	N	429	AF	0.3	0.7	0.7	0.6	0.8	0.9	0.7	133	137	141	139	135	138

| | | | POTTASIUM | | | | | | | NYHA CLASS | | | 6 MINUTE WALK | | | ECHO PARAMETERS | | | | | | |

Sr. No	Group
1	ACE-1
2	ACE-I
3	ACE-I
4	ACE-I
5	ARNI
6	ACE-I
7	ARNI
8	ACE-I
9	ACE-I
10	ARNI
11	ARNI
12	ARNI
13	ARNI
14	ACE-I
15	ACE-I
16	ACE-I
17	ACE-I
18	ACE-I
19	ACE-I
20	ACE-I
21	ACE-I
22	ACE-I
23	ACE-I
24	ARNI
25	ACE-I
26	ARNI
27	ARNI
28	ARNI
29	ACE-I
30	ACE-I
31	ACE-I
32	ACE-I
33	ACE-I
34	ACE-I
35	ACE-I
36	ACE-I
37	ACE-I
38	ACE-I
39	ACE-I
40	ACE-I
41	ACE-I
42	ACE-I
43	ACE-I
44	ACE-I
45	ACE-I
46	ACE-I
47	ACE-I
48	ARNI
49	ACE-I
50	ARNI
51	ACE-I
52	ACE-I
53	ARNI
54	ARNI
55	ACE-I
56	ACE-I
57	ACE-I
58	ACE-I
59	ACE-I
60	ACE-I
61	ARNI
62	ACE-I
63	ACE-I
64	ACE-I
65	ACE-I
66	ACE-I
67	ACE-I
68	ARNI

							PAST HISTORY								Baseline Medications												Creatinine							SODIUM					
Sr. No	Group	Name	AGE/SEX	ETIOLOGY OF HEART FAILURE	MRD.NO	COMPLAINTS	DM	HTN	CKD	CAD	COPD	CVA	THYROID	AF	Beta Blockers	ACE-I	ARBS	CCB	MRA	DIURETICS	IVABRADINE	DIGOXIN	PPI/CRT	ICD	BNP	ECG	BASELINE	2 MONTHS	4 MONTHS	6 MONTHS	8 MONTHS	10 MONTHS	12 MONTHS	BASELINE	2 MONTHS	4 MONTHS	6 MONTHS	8 MONTHS	10 MONTHS
69	ARNI	DS	58/M	ICMP	741444	DOE	Y	N	N	Y	N	N	N	N	Y	Y	N	N	Y	Y	Y	N	N	N	405	IVCD NSR	1.39	1.3	1.2	1.1	1.1	1.2	1.3	139	136	134	130	128	135
70	ARNI	BS	74/M	ICMP	741351	DOE	N	N	N	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	1310	NSR	1	0.9	0.9	1	0.9	1.1	1	139	145	138	134	136	137
71	ARNI	DS	72/M	ICMP	168495	SYNCOPE	Y	N	N	Y	N	Y	N	N	Y	Y	N	N	N	Y	N	N	N	N	617	LBBB NSR	1.4	1.3	1.4	1.6	-	-	-	130	132	136	145	-	-
72	ARNI	BSS	73/M	ICMP	288934	DOE	N	Y	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	84	NSR	0.9	0.8	0.8	0.8	0.9	0.9	0.8	142	136	134	132	131	131
73	ACE-I	KKG	62/M	ICMP	722936	OEDEMA	Y	Y	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	2570	NSR	1.4	1.2	1	0.8	0.9	0.9	0.9	139	144	142	141	140	135
74	ACE-I	NR	69/F	ICMP	366608	CHESTPAIN	Y	Y	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	84	NSR	1	1.1	1	0.8	0.8	0.9	0.9	138	135	142	136	134	138
75	ACE-I	RG	50/M	ICMP	742273	CHESTPAIN	N	N	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	153	NSR	0.8	0.9	0.8	0.8	0.8	0.8	0.9	133	138	141	140	138	137
76	ACE-I	MK	80/F	ICMP	764316	DOE	N	N	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	1760	NSR	0.8	-	-	-	-	-	-	137	-	-	-	-	-
77	ACE-I	JS	75/M	DCMP	742455	DOE	N	N	N	N	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	86	IVCD NSR	0.7	0.7	0.7	0.9	0.9	0.9	0.9	136	136	132	134	130	138
78	ACE-I	N	65/M	ICMP	746403	DOE	Y	Y	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	1220	NSR	0.8	-	-	-	-	-	-	128	-	-	-	-	-
79	ACE-I	SR	45/F	ICMP	552428	DOE	N	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	Y	N	N	N	27	NSR	0.6	0.7	0.7	0.8	0.7	0.6	0.6	139	133	132	130	128	129
80	ACE-I	K	66/F	ICMP	762113	DOE	N	N	N	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	4370	NSR	1	-	-	-	-	-	-	133	-	-	-	-	-
81	ACE-I	AS	57/M	DCMP	164226	PALPITATIONS	N	N	N	N	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	1850	NSR	1	1	1	0.8	0.9	1	1	137	143	137	130	134	131
82	ACE-I	BS	50/M	ICMP	749086	DOE	Y	N	N	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	534	LAFB NSR	1	1	0.7	0.7	0.7	0.8	1	137	136	142	140	142	146
83	ACE-I	JS	48/M	ICMP	761508	CHESTPAIN	N	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	96	NSR	0.8	0.9	0.8	0.7	0.8	0.8	0.9	135	136	134	130	134	136
84	ACE-I	BS	76/M	ICMP	75772	DOE	N	N	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	430	NSR	0.8	0.9	0.9	0.8	-	-	-	137	135	136	137	-	-
85	ARNI	KP	62/M	ICMP	757987	CHESTPAIN	N	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	679	NSR	0.8	0.8	0.9	0.8	0.9	0.9	0.8	135	140	146	136	138	140
86	ACE-I	PR	55/F	ICMP	757936	CHESTPAIN	N	Y	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	84	NSR	0.8	0.6	0.8	0.9	0.8	0.9	0.9	139	131	135	138	140	142
87	ACE-I	PR	58/F	ICMP	756675	DOE	Y	Y	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	96	NSR	0.7	0.7	0.8	0.9	0.9	0.9	0.8	133	142	143	137	140	139
88	ARNI	RK	64/F	DCMP	756621	DOE	Y	Y	N	N	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	86	NSR	0.6	0.7	0.6	0.5	0.6	0.7	0.8	139	132	136	138	145	138
89	ARNI	BK	59/F	ICMP	899744	DOE	N	N	N	Y	N	-	N	N	Y	Y	N	N	N	Y	N	N	N	N	860	NSR	0.8	0.6	0.6	0.7	0.9	0.9	1	128	139	142	143	149	138
90	ARNI	RS	65/M	ICMP	707375	DOE	N	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	1200	NSR	0.8	0.8	0.7	0.8	0.9	0.8	0.8	140	133	138	130	134	135
91	ARNI	VS	64/F	ICMP	706658	DOE	Y	Y	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	800	LBBB NSR	1	1.2	1.2	0.9	0.9	0.9	0.9	140	130	134	134	136	138
92	ARNI	SR	53/F	ICMP	606712	DOE	Y	N	N	Y	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	1310	NSR	0.6	0.6	1	1.4	0.9	0.6	1.2	135	136	140	140	142	130
93	ARNI	HS	60/M	ICMP	797676	DOE	N	N	N	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	670	NSR	0.8	0.8	0.8	0.7	0.7	0.8	0.8	144	138	135	130	132	135
94	ARNI	MK	67/F	ICMP	716893	DOE	Y	Y	N	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	560	NSR	1.5	1.3	1.2	1.3	1.11	1.2	1.1	129	136	135	136	134	135
95	ARNI	SD	70/M	ICMP	784900	DOE	Y	N	N	Y	N	N	N	Y	Y	Y	N	N	Y	Y	N	N	N	N	880	AF	0.8	0.9	0.9	1	1	1.1	1	136	138	136	136	128	129
96	ARNI	SS	50/M	ICMP	800252	PALPITATIONS	N	N	N	Y	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	1400	NSR	0.6	0.9	0.7	0.7	1	1.1	1.2	137	136	138	134	136	134
97	ARNI	SS	76/M	ICMP	564751	DOE	N	N	N	Y	N	N	N	N	Y	Y	N	Y	Y	Y	N	N	N	N	1200	NSR	1.5	1.6	1.5	1.4	1.2	1.3	1.3	138	140	136	134	139	138
98	ARNI	KS	65/M	ICMP	744116	DOE	N	Y	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	480	NSR	1.5	1.4	1.3	1.5	1.3	1.4	1.5	138	130	134	134	136	138
99	ARNI	KD	79/M	ICMP	280537	DOE	N	Y	N	Y	N	N	N	N	N	Y	N	N	Y	Y	N	N	N	N	640	NSR	1.6	1.5	1.4	1.4	1.4	1.3	1.4	137	136	138	137	134	135
100	ARNI	BS	71/M	ICMP	501585	CHESTPAIN	Y	Y	N	Y	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N	610	NSR	1.4	1.4	1.5	1.5	1.4	1.3	1.4	139	135	136	136	128	140

| | | | POTTASIUM | | | | | | | NYHA CLASS | | | 6 MINUTE WALK | | | ECHO PARAMETERS | | | | | | |

Sr. No	Group
69	ARNI
70	ARNI
71	ARNI
72	ARNI
73	ACE-I
74	ACE-I
75	ACE-I
76	ACE-I
77	ACE-I
78	ACE-I
79	ACE-I
80	ACE-I
81	ACE-I
82	ACE-I
83	ACE-I
84	ACE-I
85	ARNI
86	ACE-I
87	ACE-I
88	ARNI
89	ARNI
90	ARNI
91	ARNI
92	ARNI
93	ARNI
94	ARNI
95	ARNI
96	ARNI
97	ARNI
98	ARNI
99	ARNI
100	ARNI

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No. BFUHS/2K19p-TH/ 1872

Date 13/5/19

The Principal,
DMC, Ludhiana.

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 29.05.2019 has approved the plan of thesis of **Dr. Salil Jaura**, a student of your college for **DM Cardiology** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis

Assessment of clinical and echocardiographic features in systolic heart failure patients switched from ace inhibitors to sacubitril/valsartan

Supervisor
Dr. Naved Aslam
Prof.,
Dept. of Cardiology,
DMCH, Ludhiana.

Co-Supervisor
Dr. Shibba Takkar
Assoc. Prof.,
Dept. of Cardiology,
DMCH, Ludhiana.

The student has to submit the four copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

S P Singh

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ACE INHIBITORS TO SACUBITRIL/VALSARTAN

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

Doctorate of Medicine

In

Cardiology

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

APRIL, 2019

DR SALIL JAURA

DEPARTMENT OF CARDIOLOGY

DAYANAND MEDICAL COLLEGE & HOSPITAL

LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ACE INHIBITORS TO SACUBITRIL/VALSARTAN
For the degree of	D.M Cardiology
Name of the candidate	Dr Salil Jaura
Supervisor	Dr Naved Aslam, Professor, Department of Cardiology, DMCH, Ludhiana.
Co-supervisor	Dr Shibba Takkar Chhabra, Associate Professor, Department of Cardiology, DMCH, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: A new therapeutic class of agents acting on the RAAS and the neutral endopeptidase system has been developed [angiotensin receptor neprilysin inhibitor (ARNI)] which have been shown to improve survival in patients with HFrEF.

Aim of Study: To access effects of SACUBITRIL/VALSARTAN therapy on clinical parameters and echocardiographic features in HFReF patients as compared to ace inhibitors.

Materials & Methods: The study will be performed on 100 patients with HFReF who are already on ACE inhibitors in addition to optimal medical therapy.

Clinical Significance: This study will determine Sacubitril/Valsartan effects on LVeF and multiple measures of reverse remodeling beyond the effects of concomitant optimal medical therapy.

Keywords: Sacubitril/Valsartan, HFRef, NYHA, ace inhibitors.

(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ACE INHIBITORS TO SACUBITRIL/VALSARTAN"** exist in the Department of Cardiology, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself/herself under our supervision and guidance.

Supervisor

Dr Naved Aslam
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Co-Supervisors

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Dr. Gurpreet Singh Wander
Department of Cardiology
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Place : _____

Date : _____

APPROVAL PROFORMA
BY RESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr Salil Jaura
Department	Cardiology
Topic of Thesis	ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ACE INHIBITORS TO SACUBITRIL/VALSARTAN
Likely date of appearing in PG examination	MAY, 2021
Date of enrollment	27 AUGUST 2018
Name of Head of Department	Dr Gurpreet Singh Wander
1) Supervisor **2) Co-Supervisor(s)**	Dr Naved Aslam Dr Shibba Takkar Chhabra
Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
1. HOD Pharmacology	1. HOD Physiology
2. HOD Surgery	2. HOD Pathology
3. HOD Pathology	3. HOD Pharmacology
4. HOD Medicine	4. HOD SPM
5. Dean Academics	5. HOD Medicine
6. Vice Principal	6. HOD Surgery
	7. HOD Obst. & Gynae
	8. Legal Expert
	9. Secretary, IEC
	10. Dean Academics
	11. Vice Principal
	12. Principal

Approved: Yes / No

Chairperson
Research Committee

Approved: Yes / ~~No~~

Chairperson
Ethics Committee

Chairperson
Research Committee
Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

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2	NAME OF THE INSTITUTE	DAYANAND MEDICAL COLLEGE AND HOSPITAL LUDHIANA
3	COURSE OF STUDY AND SUBJECT	DM CARDIOLOGY
4	DATE OF ADMISSION OF COURSE	27 AUGUST 2018
5	TITLE OF THE TOPIC	ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ACE INHIBITORS TO SACUBITRIL/VALSARTAN

6 BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.

The main terminology used to describe HF is historical and is based on measurement of the LVEF. HF comprises a wide range of patients, from those with normal LVEF [typically considered as ≥50%; HF with preserved EF (HFpEF)] to those with reduced LVEF [typically considered as <40%; HF with reduced EF (HFrEF)]. Patients with an LVEF in the range of 40–49% represent a 'grey area', which is now defined as HFmrEF.[1]

The prevalence of HF is approximately 1–2% of the adult population in developed countries, rising to ≥10% among people >70 years of age.[2] The lifetime risk of HF at age 55 years is 33% for men and 28% for women.[3] The 12-month all-cause mortality rates for hospitalized and stable/ambulatory HF patients were 17% and 7%, respectively.[4] In patients with HF (both hospitalized and ambulatory), most deaths are due to cardiovascular causes, mainly sudden death and worsening HF. All-cause mortality is generally higher in HFrEF than HFpEF.[5]

The NYHA functional classification has been used to describe the severity of symptoms and exercise intolerance.[6] For patients presenting with symptoms or signs for the first time, non-urgently in primary care or in a hospital

outpatient clinic , the probability of HF should first be evaluated based on the patient's prior clinical history [e.g. coronary artery disease (CAD), arterial hypertension, diuretic use], presenting symptoms (e.g. orthopnoea), physical examination (e.g. bilateral oedema, increased jugular venous pressure, displaced apical beat) and resting ECG. If all elements are normal, HF is highly unlikely and other diagnoses need to be considered. If at least one element is abnormal, plasma NPs should be measured, if available, to identify those who need echocardiography (an echocardiogram is indicated if the NP level is above the exclusion threshold or if circulating NP levels cannot be assessed).[7] Transthoracic echocardiography (TTE) is the method of choice for assessment of myocardial systolic and diastolic function of both left and right ventricles. For measurement of LVEF, the modified biplane Simpson's rule is recommended.[8] Measurement of regional wall motion abnormalities might be particularly relevant for patients suspected of CAD or myocarditis. Doppler techniques allow the calculation of haemodynamic variables, such as stroke volume index and cardiac output, based on the velocity time integral at the LV outflow tract area.

Neuro-hormonal antagonists (ACEIs, MRAs and beta-blockers) have been shown to improve survival in patients with HFrEF and are recommended for the treatment of every patient with HFrEF, unless contraindicated or not tolerated. A new therapeutic class of agents acting on the RAAS and the neutral endopeptidase system has been developed [angiotensin receptor neprilysin inhibitor (ARNI)]. The first in class is LCZ696, which is a molecule that combines the moieties of valsartan and sacubitril (neprilysin inhibitor) in a single substance. By inhibiting neprilysin, the degradation of NPs, bradykinin

and other peptides is slowed. High circulating A-type natriuretic peptide (ANP) and BNP exert physiologic effects through binding to NP receptors and the augmented generation of cGMP, thereby enhancing diuresis, natriuresis and myocardial relaxation and anti-remodelling. ANP and BNP also inhibit renin and aldosterone secretion. Selective AT1-receptor blockade reduces vasoconstriction, sodium and water retention and myocardial hypertrophy.[9] (SACUBITRIL/VALSARTAN) has been shown to be superior to an ACEI (enalapril) in reducing the risk of death and of hospitalization for HF in a single trial with strict inclusion/exclusion criteria[10] Sacubitril/valsartan is therefore recommended to replace ACEIs in ambulatory HFrEF patients who remain symptomatic despite optimal therapy and who fit these trial criteria. The above medications should be used in conjunction with diuretics in patients with symptoms and/or signs of congestion. The use of diuretics should be modulated according to the patient's clinical status.

Oral bioavailability of SACUBITRIL/VALSARTAN is >=60%.Steady-state is reached in 3 days. It is highly protein bound 94-97%. Volume of distribution is 75 L for sacubitril and 103 L for valsartan. Sacubitril component is primarily excreted in the urine (52-68%) and feces (37-48%) Valsartan component is primarily excreted in the feces (86%) and to a lesser extent in the urine (13%). Despite the superiority of sacubitril/valsartan over enalapril in the PARADIGM-HF trial, some relevant safety issues remain when initiating therapy with this drug in clinical practice. Symptomatic hypotension was more often present in the sacubitril/valsartan group although there was no increase in the rate of discontinuation. Sacubitril/valsartan tends to increase risk of angioedema. If angioedema occurs, SACUBITRIL/VALSARTAN (sacubitril/valsartan) should

be discontinued and should not be rechallenged. SACUBITRIL/VALSARTAN should not be used in those with a history of angioedema related to previous ACE inhibitor or ARB therapy. If switching to or from an ACE inhibitor, a 36-hour washout period is required between drugs. Combined treatment with an ACEI (or ARB) and sacubitril/valsartan is contraindicated. Being a RAAS blocking agent; SACUBITRIL/VALSARTAN (sacubitril/valsartan) may cause impaired renal function in high risk individuals including those with renal artery stenosis. Because of RAAS blockade, sacubitril/valsartan may cause hyperkalemia. There are additional concerns about its effects on the degradation of beta-amyloid peptide in the brain, which could theoretically accelerate amyloid deposition[11]

6.2 REVIEW OF LITERATURE

John J.V. McMurray et al in year 2014, compared the angiotensin receptor–neprilysin inhibitor SACUBITRIL/VALSARTAN with enalapril in patients who had heart failure with a reduced ejection fraction. In this double-blind trial, they randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either SACUBITRIL/VALSARTAN (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes. The trial was stopped early, according to prespecified rules, after a median followup of 27 months, because the boundary for an overwhelming benefit with SACUBITRIL/VALSARTAN had been crossed. As compared with enalapril, SACUBITRIL/VALSARTAN also reduced the risk of hospitalization for heart failure by 21% ($P<0.001$) and decreased the symptoms and physical limitations of heart failure ($P = 0.001$). The SACUBITRIL/VALSARTAN group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group. SACUBITRIL/VALSARTAN was superior to enalapril in reducing the risks of death and of hospitalization for heart failure.[12]

A study was conducted by R. De Vecchis et al in year 2017 which was a retrospective cohort study aimed to assess the effects of sacubitril/valsartan in addition to a beta-blocker and mineral receptor antagonist (MRA) in a group of HFREF patients with NYHA class II-III HF vs. conventional therapy (ACE

inhibitor or angiotensin II receptor blocker added to a beta-blocker plus an MRA) administered to a control group of HFREF patients with comparable clinical features. In both groups, treatment was supplemented by a loop diuretic, usually furosemide, at variable doses. The primary outcomes were all-cause death and HF hospitalizations. Safety outcomes were symptomatic hypotension, angioedema, hyperkalemia, and worsening renal function. It was concluded that Sacubitril/valsartan offered strong protection against all-cause death and HF hospitalizations at 6 months without any significant side effects.[13]

Aws Almufleh et al in year 2017 performed a single center, retrospective, cohort study of HFrEF patients (n=48) who were treated with Sacubitril/Valsartan for a median duration of 3 months (Interquartile range 2-6 months). Clinical and echocardiographic parameters were reviewed at three time points (pre-baseline which was median of 18 months before starting Sacubitril/Valsartan, baseline before treatment started, and post-Sacubitril/Valsartan). Sacubitril/Valsartan use was associated with an average 5% (±1.2) increase in EF, from a mean baseline of 25.33% to 30.14% ($p<0.001$) with a median duration of treatment 3 months. There was a 3.36 mm reduction in left ventricular end-systolic diameter ($p=0.04$), a 2.64 mm reduction in left ventricular end-diastolic diameter ($p=0.02$), and a 14.4 g/m2 reduction in left ventricular mass index ($p<0.01$). It was concluded that Sacubitril/Valsartan was found to improve EF and multiple measures of reverse remodeling beyond the effects of concomitant optimal medical therapy.[14]

Masanobu Ishii et al conducted a study in year 2017 in which Wild-type mice subjected to ligation of left anterior descending artery were randomly allocated to the vehicle, enalapril, or SACUBITRIL/VALSARTAN group 1 day after MI. The present study showed that SACUBITRIL/VALSARTAN can prevent cardiac rupture after MI, probably due to the suppression of pro-inflammatory cytokines, matrix metalloproteinase-9 activity and aldosterone production, and enhancement of natriuretic peptides in mice. These findings suggest the mechanistic insight of cardioprotective effects of SACUBITRIL/VALSARTAN against acute MI, resulting in the belief that SACUBITRIL/VALSARTAN might be useful clinically to improve survival after acute MI.[15]

Eric J. Velazquez, M.D., et al in year 2018 enrolled patients with heart failure with reduced ejection fraction who were hospitalized for acute decompensated heart failure at 129 sites in the United States. After hemodynamic stabilization, patients were randomly assigned to receive sacubitril–valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) or enalapril (target dose, 10 mg twice daily). The primary efficacy outcome was the time-averaged proportional change in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration from baseline through weeks 4 and 8. It was concluded that the initiation of sacubitril–valsartan therapy led to a greater reduction in the NT-proBNP concentration than enalapril therapy. Rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two groups.[16]

Wachter and colleagues in year 2018 randomly assigned 1,002 patients (mean age, 67 years; 75% men; mean left ventricular ejection fraction, 29%) hospitalized for acute decompensated HF with reduced EF to sacubitril/valsartan after being hemodynamically stabilized while still in the hospital or after discharge. The primary endpoint was proportion of patients achieving the target dose of sacubitril/valsartan 200 mg twice daily at 10 weeks after randomization. Secondary endpoints included discontinuation due to drug-related adverse events and tolerability of different sacubitril/valsartan doses. The primary endpoint was achieved in 45% of the predischarge group and 50.4% of the post discharge group (relative risk ratio [RRR] = 0.893; 95% CI, 0.783-1.019). Study drug discontinuation occurred in 4.5% of the predischarge group and 3.5% of the post discharge group (RRR = 1.287; 95% CI, 0.692-2.395).Rates of adverse events, serious adverse events and death did not significantly differ between the groups. The most important finding is that it is as safe and efficacious to start sacubitril/valsartan in the hospital as in the outpatient setting, whether the patient is on a high dose or a medium dose of the drug.[17]

6.3 AIMS AND OBJECTIVES OF THE STUDY

1. To study clinical and echocardiographic features in systolic heart failure patients on ACE INHIBITORS.

2. Assessment of clinical and echocardiographic features when patients were switched over from ACE INHIBITORS to SACUBITRIL/VALSARTAN therapy and comparison between two groups.

7.0 MATERIALS AND METHODS

The study population will consist of 100 patients with HFReF patients who are already on ace inhibitors in addition to optimal medical therapy enrolled from DMC & HOSPITAL.

These patients will be analysed at baseline by NYHA FUNCTIONAL CLASS , 6 minute walk test and transthoracic echocardiography. Imaging data will be analysed for LV dimensions and volume.

These patients will be followed up for six months and reassessed for NYHA class, 6 minute walk test and Transthoracic echocardiography.

Thereafter patients will be given option for sacubitril/valsartan therapy and those who will opt, will be switched over from ace inhibitor to sacubitril/valasartan therapy on maximum tolerated dose after stopping ace inhibitors for 36 hours. All patients will be followed up for additional 6 months and thereafter will be reassessed for NYHA class, 6 minute walk test and TTE.

At the end of 1 year comparison will be made between patients who were switched over to sacubitril/valasartan therapy versus those patients who were not able to shift to sacubitril/valasartan therapy and hence were continued on ace-inhibitors. Also comparison will be made between the clinical parameters and echocardiographic features at 6 months versus at 1 year.

The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent of heart failure.[18] It places patients in one of four categories based on how much they are limited during physical activity. The 6-min walk test (6 MWT) is a submaximal exercise test that entails measurement of distance walked over a span of 6 minutes. The 6 MWT

provides information regarding functional capacity, response to therapy and prognosis across a broad range of chronic cardiopulmonary conditions.[19]

TTE will be used for measurement of LV dimensions and volume. The most commonly used 2D method for volume measurements is the biplane method of discs (modified simpson's rule).[20] The principle underlying this method is that the total LV volume is calculated from the summation of a stack of elliptical disks. LV volumes will be measured from apical 4 and/or apical 2 chamber views, tracing the endocardial border of the LV. If there is no wall motion abnormality, the EF can be estimated from one view only, apical 4 chamber or apical 2 chamber view. The ejection fraction is calculated from the difference between end-diastolic and end-systolic LV volume, divided by the end-diastolic LV volume:

$$EF = \frac{\text{End-diastolic volume - end-systolic volume}}{\text{end-diastolic volume}}$$

7.1 SOURCE OF DATA:

Data collection will be done by analyzing the patients with HFReF enrolled from DMC & HOSPITAL at baseline, 6 months and 1 year.

7.2 METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA : Patients with HFReF (EF<40%).

EXCLUSION CRITERIA: 1. Symptomatic hypotension

2. An estimated glomerular filtration rate (eGFR) below 30 ml per minute per 1.73 m2 of body-surface area,

3. Serum potassium level of more than 5.5 mmol per liter.

4. History of angioedema or unacceptable side effects during receipt of ACE inhibitors or ARBs.

OUTCOME: It is hypothesized that sacubitril/valsartan will improve clinical profile and echocardiographic parameters beyond the effects of concomitant optimal medical therapy.

STATISTICAL ANALYSIS: After data has been collected, it will be subjected to analysis using appropriate statistical methods. The data obtained at various stages of the study will be compared taking into account the specific objectives of the study.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

NO

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

ATTACHED HEREWITH

8.0 LIST OF REFERENCES

1. Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, et al. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. JACC Heart Fail. 2014;2:97-112.
2. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007;93:1137-46.
3. Bleumink GS, Knetsch AM, Sturkenboom MCJM, Straus SMJM, Hofman A, Deckers JW, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam study. Eur Heart J England. 2004;25:1614-9.
4. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, et al. EUR Observational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail. 2013;15:808-17.
5. Pocock SJ, Ariti CA, McMurray JJV, Maggioni A, Køber L, Squire IB, et al,. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013;34:1404-13.
6. McMurray JJ V. Clinical practice. Systolic heart failure. N Engl J Med. 2010;3623:228-38.
7. Krishnaswamy P, Lubien E, Clopton P, Koon J, Kazanegra R, Wanner E. Utility of B-natriuretic peptide levels in identifying patients with left ventricular systolic or diastolic dysfunction. Am J Med. 2001;111:274-9.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the

European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16:233-70.

9. King JB, Bress AP, Reese AD, Munger MA. Neprilysin inhibition in heart failure with reduced ejection fraction: a clinical review. Pharmacother J Hum Pharmacol Drug Ther. 2015;35:823-37.
10. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993-1004.
11. Vodovar N, Paquet C, Mebazaa A, Launay J-M, Hugon J, Cohen-Solal A. Neprilysin, cardiovascular, and Alzheimer's diseases: the therapeutic split? Eur Heart J. 2015;36:902-5.
12. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med. 2014;371:993-04.
13. De Vecchis R, Ariano C, Di Biase G, Noutsias M. Sacubitril/valsartan for heart failure with reduced left ventricular ejection fraction: A retrospective cohort study. Herz. 2018 Jan 19. doi: 10.1007/s00059-017-4671-1
14. Almufleh A, Marbach J, Chih S, Stadnick E, Davies R, Liu P, et al. Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in heart failure with reduced ejection fraction patients. Am J Cardiovasc Dis. 2017;7:108-13.
15. Ishii M, Kaikita K, Sato K, Sueta D, Fujisue K, Arima Y, et al. Cardioprotective Effects of SACUBITRIL/VALSARTAN (Sacubitril/Valsartan) After Experimental Acute Myocardial Infarction. JACC. 2017;2:655-68.

16. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin–Neprilysin Inhibition in acute decompensated heart failure. N Engl J Med. 2019;380:539-48.
17. Wachter R. Presented at: European Society of Cardiology Congress; Munich; 2018. (Abstract P6531).
18. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-6.
19. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation, 3rd edition. Philadelphia: Lippincott, Williams & Wilkins; 1999.
20. Lang RM, Bierig M, Devereux RB. Recommendations for chamber quantification. J Am Soc Echocardiogr. 2005;18:1440-63.

PROFORMA

Name: GROUP:

Age:

Sex:

MRD No.:

Address:

Chief complaints:

Brief History of Present:

Illness

Past History

DIABETES MELLITUS:

HYPERTENSION:

CKD:

Personal History

Smoker/Non Smoker:

Alcoholic/Non-Alcoholic:

Veg. / non veg:

Medications at baseline:

Signature of Candidate Signature of Supervisor

Family History

Diabetes Mellitus:

Hypertension:

Examination

GPE

Height:

Weight:

Anemia :

Cyanosis :

Jaundice :

Oedema :

JVP-

Pulse :

Blood Pressure :

Respiratory Rate:

Temperature :

System Examination

-Abdomen

-CVS:

-Chest:

-CNS:

Investigations

CBC

FBS/RBS

BNP

ECG

RFT every 2months

Signature of Candidate

Signature of Supervisor

	Baseline	2 months	4 months	6 months	8 months	10 months	12 months
Na							
K							
Cl							
Urea							
Creat							

	Baseline	6 months	1 year
NYHA Class			
6 Minute walk distance			
ECHO Parameters: LV EJECTION FRACTION LV Internal Diameter(systole) LV Internal Diameter(diastole) LA Diameter MV E/A velocity ratio Mitral regurgitation severity PASP TAPSE			

Maximum Tolerated Dose of sacubitril/valsartan:

Signature of Candidate

Signature of Supervisor

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....

.....am willing to participate in the study **"ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ACE INHIBITORS TO SACUBITRIL/VALSARTAN "** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

.....
Signature of the Witness

Name:

.....
Signature of the patient

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य "**ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ACE INHIBITORS TO SACUBITRIL/VALSARTAN** " में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"ASSESSMENT OF CLINICAL AND ECHOCARDIOGRAPHIC FEATURES IN SYSTOLIC HEART FAILURE PATIENTS SWITCHED FROM ACE INHIBITORS TO SACUBITRIL/VALSARTAN " ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____ _____

ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

_____

ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

_____

ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ